UNIVERSITY OF HAWAII
LIBRARY
OCT 31 '51

THE BULLETIN OF Mathematical BIOPHYSICS

SEPTEMBER 1951

A NOTE ON THE THEORY OF COMMUNICATION THROUGH SOCIAL CHANNELS—*N. Rashevsky* - - - - - - - - - - 139

A NOTE ON IMITATIVE BEHAVIOR AND INFORMATION—*N. Rashevsky* - - - - - - - - - - - - - - 147

A SUGGESTED CHAIN PROCESS FOR RADIATION DAMAGE—*A. T. Reid and H. G. Landau* - - - - - - - - - 153

APPLICATIONS OF MATRIX ALGEBRA TO COMMUNICATION NETS—*Alfonso Shimbel* - - - - - - - - - - - - 165

"ADDITION" AND "MULTIPLICATION" THEOREMS FOR THE INPUTS OF TWO NEURONS CONVERGING ON A THIRD—*Anatol Rapoport* 179

CONTRIBUTIONS TO THE MATHEMATICAL BIOLOGY OF EXCITATION WITH PARTICULAR EMPHASIS ON CHANGES IN MEMBRANE PERMEABILITY AND ON THRESHOLD PHENOMENA—*George Karreman* - - - - - - - - - - - 189

THE UNIVERSITY OF CHICAGO PRESS · CHICAGO · ILLINOIS

VOLUME 13 · · · · · NUMBER 3

9

THE BULLETIN OF MATHEMATICAL BIOPHYSICS

Editor:

N. Rashevsky

Associate Editors:

H. D. Landahl; Anatol Rapoport

The Bulletin is devoted to publications of research in Mathematical Biology, as described on the inside back cover.

The Bulletin is published by the University of Chicago at the University of Chicago Press, 5750 Ellis Avenue, Chicago 37, Illinois, quarterly, in March, June, September, December. ¶The subscription price is $7.50 per year, the price of single copies is $2.25. Orders for service of less than a full year will be charged at the single-copy rate. ¶Patrons are requested to make all remittances payable to the University of Chicago Press in postal or express money orders or bank drafts.

The following is an authorized agent:

For the British Empire, except North America, India, and Australasia: The Cambridge University Press, Bentley House, 200 Euston Road, London, N.W. 1. Prices of yearly subscriptions and of single copies may be had on application.

Claims for missing numbers should be made within the month following the regular month of publication. The publishers expect to supply missing numbers free only when losses have been sustained in transit, and when the reserve stock will permit.

Business Correspondence should be addressed to the University of Chicago Press, Chicago 37, Ill.

Communications for the editor and manuscripts should be addressed to N. Rashevsky, Editorial Office of *The Bulletin of Mathematical Biophysics*, 5741 Drexel Avenue, Chicago 37, Ill.

NOTICE TO SUBSCRIBERS

If you change your address, please notify us and your local postmaster immediately. The Post Office does not forward third-class mail.

PRINTED BY THE DENTAN PRINTING COMPANY . . . COLORADO SPRINGS, COLORADO

BULLETIN OF
MATHEMATICAL BIOPHYSICS
VOLUME 13, 1951

A NOTE ON THE THEORY OF COMMUNICATION THROUGH SOCIAL CHANNELS

N. RASHEVSKY
COMMITTEE ON MATHEMATICAL BIOLOGY
THE UNIVERSITY OF CHICAGO

In a previous paper (Bull. Math. Biophysics, 12, 215, 1950) a theory of transmission of information through a chain of individuals was developed. It was assumed that each individual can exhibit only two mutually exclusive reactions, which serve as signals, thus transmitting to his neighbor one bit of information per signal. In the present paper the theory is generalized to the case of any number m of mutually exclusive reactions, giving thus $\log_2 m$ bits per signal. The general character of the process of transmission remains very much the same as before; the mathematical expression becoming, however, more complicated.

In a previous paper (Rashevsky, 1950b; hereinafter referred to as *loc. cit.*) we studied the transmission of communication through a chain of individuals in which each individual is capable of only one out of two mutually exclusive reactions used as signals. Thus one individual can transmit at most one bit of information per signal. We shall outline here a generalization of the theory to the case in which each individual has the choice of one out of m possible reactions. The study of this case requires a generalization of H. D. Landahl's (1937) theory of cross-inhibited parallel chains with fluctuating excitations from two to m chains. A direct exact approach to that problem leads to great difficulties (Rashevsky, 1950a). Landahl (1941a,b) in his theory of learning has, however, suggested an approximate approach, which we shall use here.

With a Laplacian distribution of random fluctuations the expression for a wrong response R_2 to the stimulus S_1 in the two-stimuli case is given by (Rashevsky, 1948, chap. xli):

$$P_w = \tfrac{1}{2} e^{-k(\varepsilon_1 - \varepsilon_2)} \tag{1}$$

where the notations are the same as in the above reference. Landahl (1941a,b) [cf. also Rashevsky, 1948, chap. xli] suggests for the case of m stimuli the following expression for the probability P_w of a wrong response $R_i \, (i \neq 1)$ to the stimulus S_1

$$P_w = \frac{m-1}{m} e^{-k(\varepsilon_1 - \bar{\varepsilon})}, \tag{2}$$

where

$$\bar{\varepsilon} = \frac{\varepsilon_2 + \varepsilon_3 + \cdots\cdot + \varepsilon_m}{m-1}. \tag{3}$$

When all the ε_i's are equal, $P_1 = \dfrac{m-1}{m}$, as should be the case.

We shall assume in general for the probability P_i of a response R_i when all ε_k's are different, the expression

$$P_i = 1 - P_w = 1 - \frac{m-1}{m} e^{-k[\varepsilon_i - \bar{\varepsilon}^{(i)}]} \tag{4}$$

with

$$\bar{\varepsilon}^{(i)} = \frac{\varepsilon_1 + \varepsilon_2 + \cdots\cdot \varepsilon_{i-1} + \varepsilon_{i+1} + \cdots\cdot \varepsilon_m}{m-1}. \tag{5}$$

Due to the approximate nature of expression (4), $\sum P_i$ is in general not equal to 1. It may be possible to normalize expression (4) appropriately, so as to fulfill the requirement $\sum P_i = 1$.

If, instead of a Laplacian distribution of the fluctuations, a normal distribution is used, then we have, for the case of two stimuli ($\varepsilon_1 > \varepsilon_2$) (Landau, 1950):

$$P_c = G\left(\frac{\varepsilon_1 - \varepsilon_2}{\sigma}\right), \tag{6}$$

where

$$G\left(\frac{x}{\sigma}\right) = \frac{1}{\sqrt{2\pi}\,\sigma} \int_{-\infty}^{x} e - \frac{x^2}{2\sigma^2}\, dx. \tag{7}$$

In line with Landahl's generalization, we shall assume the following expression:

Let κ_m denote the root of the equation

$$G\left(\frac{\kappa_m}{\sigma}\right) = \frac{1}{m}. \tag{8}$$

The quantity κ_m is always negative for $m > 2$. Then for the probability P_i of response R_i put

$$P_i = G\left(\frac{\kappa_m + \varepsilon_i - \varepsilon^{(i)}}{\sigma}\right). \qquad (9)$$

When all ε's are equal to $(\varepsilon_i = \bar{\varepsilon}')$ we have $P_i = \frac{1}{m}$, as should be the case. As ε_i tends to ∞, P_i tends to 1.

Let the ε_i's represent permanent excitations at the corresponding connections. They are present in the absence of any external stimuli S_i. If such external stimuli are present, the corresponding ε_i is increased by an amount proportional to S_i (neglecting peripheral thresholds). With a proper choice of units we now have, instead of ε_i, the quantity $\varepsilon_i + S_i$. Hence equation (9) becomes

$$P_i = G\,\frac{\kappa_m + \varepsilon_i + S_i - (\overline{\varepsilon}^{(i)} + \overline{S}^{(i)})}{\sigma}, \qquad (10)$$

with

$$S^{(i)} = \frac{S_1 + S_2 + \cdots\cdot S_{i-1} + S_{i+1} + \cdots\cdot + S_m}{m-1}. \qquad (11)$$

Expression (10) is of course only a rough approximation.

As in *loc. cit.* we shall consider that the sight of a reaction R_i performed by another individual acts as a stimulus S_i on the given individual. We again limit ourselves to the rather artificial assumption that all reactions, and hence all stimuli, are of the same intensity S. If now in a chain of individuals, the $(n - 1)$st individual makes a reaction R_i, this reaction acts as a stimulus S_i of intensity S on the nth individual. Since we assume that only one out of m reactions can be produced at a time, the nth individual is subject to a stimulus $S_i = S$, while all other S_k's $(k \neq i)$ are equal to zero. The probability of his producing the reaction R_i, as a result of this is, therefore, given, according to (10), by

$$P_{ii} = G\left(\frac{\kappa_m + \varepsilon_i + S - \overline{\varepsilon}^{(i)}}{\sigma}\right). \qquad (12)$$

On the other hand, the probability P_{ik} that the nth individual will produce the reaction R_k $(k \neq i)$, when the $(n - 1)$th produces R_i, is given by

$$P_{ik} = G\left(\frac{\kappa_m + \varepsilon_k - \varepsilon^{(k)} - \dfrac{S}{m-1}}{\sigma}\right), \tag{13}$$

because now, according to (11),

$$\bar{S}^{(k)} = \frac{S}{m-1}. \tag{14}$$

If all ε_i's are equal, so that there is no natural bias in favor of one or another reaction, we have, instead of (12) and (13),

$$P_{ii} = G\left(\frac{\kappa_m + S}{\sigma}\right) \tag{15}$$

and

$$P_{ik} = G\left(\frac{\kappa_m - \dfrac{S}{m-1}}{\sigma}\right). \tag{16}$$

In this case all P_{ik}'s $(i \neq k)$ are equal, as should physically be the case. If m is large and S is large, then P_{ii} is close to 1, while P_{ik} is very small (Fig. 1).

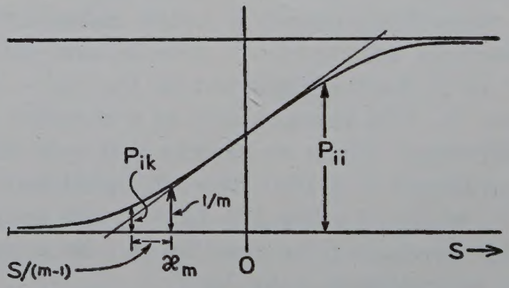

FIGURE 1

For not too large values of S we may derive the following approximate expressions by approximating the curve of Fig. 1 by a straight line

$$\frac{1}{2} + \frac{S}{\sqrt{2\pi}\,\sigma}; \qquad -\sigma\sqrt{\pi/2} < S < \sigma\sqrt{\pi/2} \tag{17}$$

whose ordinate is equal to 1/2 for $S = 0$. Then, from (15) and (16)

$$P_{ii} = \frac{1}{2} + \frac{\kappa_m + S}{\sqrt{2\pi}\,\sigma} \tag{18}$$

and

$$P_{ik} = \frac{1}{2} + \frac{\kappa_m - \dfrac{S}{m-1}}{\sqrt{2\pi}\,\sigma}. \tag{19}$$

Hence

$$\Delta = P_{ii} - P_{ik} = \frac{S}{\sqrt{2\pi}\,\sigma}\,\frac{m}{m-1}. \tag{20}$$

In general different individuals in the chain will have different biases ε_i's. Hence their P_{ii}'s and P_{ik}'s will be different. We shall denote by $P_{ii}(n)$ and $P_{ik}(n)$ the corresponding values for the nth individual. Denote by $p_k(n)$ the probability of reaction R_k by the nth individual. Since the possible reactions of the $(n-1)$st individual act as stimuli on the nth individual, we have:

$$\begin{aligned} p_k(n) &= p_1(n-1)P_{1k}(n) + p_2(n-1)P_{2k}(n) \\ &+ \cdots p_m(n-1)P_{mk}(n). \end{aligned} \tag{21}$$

Since

$$\sum_1^m p_r(n-1) = 1, \tag{22}$$

therefore, putting

$$\begin{aligned} P_{ik}(n) - P_{mk}(n) &= A_{ik}(n); \\ P_{mk}(n) &= B_k(n) \end{aligned} \tag{23}$$

we may write expression (21) in the following way:

$$\begin{aligned} p_k(n) &= p_1(n-1)A_{1k}(n) + p_2(n-1)A_{2k}(n) + \cdots \\ &+ p_{m-1}(n-1)A_{m-1,k}(n) + B_k(n). \end{aligned} \tag{24}$$

Introducing matrix notations we have:

$$\boldsymbol{p}(n) = \boldsymbol{p}(n-1)\boldsymbol{A}(n) + \boldsymbol{B}(n). \tag{25}$$

This recursion formula is satisfied formally by the matrix expression

$$\boldsymbol{p}(n) = \boldsymbol{p}(0)\boldsymbol{A}(1)\boldsymbol{A}(2)\cdots\boldsymbol{A}(n)\left(\boldsymbol{I} + \sum_1^n \frac{\boldsymbol{B}(k)}{\boldsymbol{p}(0)\boldsymbol{A}(1)\cdots\boldsymbol{A}(k)}\right), \tag{26}$$

in which $\boldsymbol{I}$ denotes the unity matrix. When the expressions P_{ii} and P_{ik} $(k \neq i)$ are independent of n, then all the square matrices $\boldsymbol{A}_n$ are equal to $\boldsymbol{A}$, and all the row matrices $\boldsymbol{B}_n$ are equal to $\boldsymbol{B}$, and expression (26) reduces to

$$\boldsymbol{p}(n) = \boldsymbol{p}(0)\boldsymbol{A}^n + \boldsymbol{B}\frac{\boldsymbol{I} - \boldsymbol{A}^n}{\boldsymbol{I} - \boldsymbol{A}}. \tag{27}$$

We may now, as in *loc cit.,* ask the question as to what is the probability of the nth individual producing any reaction R_r, if the zeroth individual produces a given reaction R_i, which, without loss of generality, may be put as R_1. In this case the row matrix $\boldsymbol{p}(0)$ is simply equal to $100 \cdots$.

For purposes of obtaining simple closed expressions even the restricted expression (27) is still rather inconvenient. We may, however, draw some important conclusions from it.

As in equation (46) of *loc. cit.,* we may interpret the first term of the right side of (27) as due to the transmitted information, while the second term may be interpreted as due to channel noise. Equation (44) of *loc cit.* shows that for $m = 2$ the probability of receiving a signal different from that given at the input is determined only by the channel noise. In the present more general case of $m > 2$ this is not so. If we denote by $(\boldsymbol{A}^n)_{ik}$ the ikth element of the matrix $\boldsymbol{A}^n$ and remember that $p_1(0) = 1$, $p_r(0) \neq 0$; $(r \neq 1)$, then we find from equation (27):

$$p_r(n) = p_1(0)\,(A^n)_{1r} + \left(B\frac{1 - A^n}{I - A}\right)_r . \tag{28}$$

Equation (28) shows that $p_1(0)$ contributes in general to any $p_r(n)$, $r \neq 1$. In other words the occurrence of any reaction R_r, different from R_1, is due in general to transmission as well as to channel noise.

If, at the input end, R_1 is always produced, so that $p_1(0) = 1$, and, if we are interested in the probability $p_1(n)$ of R_1 at the output end, we see that the part of $p_1(n)$ which is due to transmission is given by

$$p_1(n) = (\boldsymbol{A}^n)_{11} . \tag{29}$$

The element $(\boldsymbol{A}^n)_{11}$ of the matrix A is an nth degree polynomial in the A_{ik}'s. Since $A_{ik} < 1$, we see that the transmitted information decreases with n, tending to zero as n tends to infinity.

Because of the formal analogy of equation (27) and of equation (44) of *loc. cit.* we can derive in a similar way as before the expression for the *a posteriori* probability of R_1 at the input, when R_1 is received at the output. We find now, using notations similar to those used in *loc. cit.*,

$$\tilde{p}_n = \frac{p_{cn} + mp_{in}}{mp_n}. \tag{30}$$

Hence as n increases, $\tilde{p}_n$ tends to $1/m$.

A rather interesting case to study would be the following. Suppose that all possible reactions R_k can be arranged linearly in order of their similarity. The similarity may be either a phonetic or a semantic one. The determination of the similarity may be made by standard psychometric methods. The following situation is quite plausible. If the $(n-1)$st individual makes a reaction R_i, then the probability that the nth individual will make a reaction R_l $(l \neq i)$ will be the greater, the smaller the similarity between R_i and R_l; that is, the greater the distance between R_i and R_l in their linear arrangement. A neurological mechanism, providing for this, can be readily suggested. Mathematically we may express the situation by taking the matrix $\boldsymbol{P}$ in expression (21) to be symmetric, and by putting

$$P_{ik} = P_{ki} = \eta\, e^{-\lambda|k-i|}. \tag{31}$$

The rows and columns of the matrix A now become geometric series, the ratios of which are powers of $e^{-\lambda}$. It may perhaps be possible to find at least approximate closed expressions for $p_k(n)$ in that case and study the effect of λ on the decrement in transmission.

The author is indebted to Dr. George Karreman for a careful check of this paper.

LITERATURE

Rashevsky, N. 1948. *Mathematical Biophysics.* Rev. Ed. Chicago: University of Chicago Press.

——— 1950a. "Psychophysical Discrimination with more than Two Stimuli." *Bull. Math. Biophysics,* 12, 215–20.

——— 1950b. "Some Bio-Sociological Aspects of the Mathematical Theory of Communication." *Ibid.,* 12, 359–78.

Landahl, H. D. 1938. "A Contribution to the Mathematical Biophysics of Psychophysical Discrimination." *Psychometrika,* 3, 107–25.

——— 1941a. "Studies in the Mathematical Biophysics of Discrimination and Conditioning I." *Bull. Math. Biophysics,* 3, 13–26.

——— 1941b. "Studies in the Mathematical Biophysics of Discrimination and Conditioning II: Special Case: Errors, Trials, and Number of Possible Responses." *Bull. Math. Biophysics,* 3, 71–7.

Landau, H. G. 1950. "Note on the Effect of Imitation in Social Behavior." *Bull. Math. Biophysics,* 3, 221–35.

BULLETIN OF
MATHEMATICAL BIOPHYSICS
VOLUME 13, 1951

A NOTE ON IMITATIVE BEHAVIOR AND INFORMATION

N. Rashevsky
Committee on Mathematical Biology
The University of Chicago

The equations for imitative behavior developed previously indicate that the imitation effect increases with the number N_0 of individuals in the social group. In this note it is pointed out that the above conclusion holds only for not too large values of N_0. The above conclusion is based on the tacit assumption that each individual is completely informed about the behavior adopted by every other individual. If, however, N_0 becomes very large, the information per individual decreases. As a result of this, the effects of imitation either increase with N_0 less rapidly or actually become independent of N_0.

The basic equation of imitative behavior, as developed previously (Rashevsky, 1951a), with the same notations as used before is:

$$\frac{d\psi}{dt}=A(X-Y)-a\psi. \tag{1}$$

The quantity $X-Y$, which is the difference between the number X of all individuals who exhibit behavior R_1 and the number Y of all individuals who exhibit behavior R_2, acts as a stimulus to imitate behavior R_1. Since

$$X+Y=N_0, \tag{2}$$

the largest possible value of $X-Y$ is N_0. With increasing ψ the quantity $X-Y$ tends asymptotically to N_0, and, if all other parameters are kept constant, the value of $X-Y$ for any particular ψ is proportional to N_0.

Equation (1) holds, however, only with the tacit assumption that each individual actually knows the amounts X and Y. For relatively small values of N_0 this may be the case. As N_0 increases, an individual is likely to have complete information only about those other individuals who are in his immediate neighborhood. Generalizing the concepts used in *loc. cit.*, considering X and Y now as functions of the coordinates x',y', and introducing a function of the distance

$$r=\sqrt{(x-x')^2+(y-y')^2}$$

between the given individual located at x,y and an individual at x',y', we obtain an integrodifferential equation (Rashevsky, 1950a). This equation, as it has been shown, leads to a nonuniform distribution of behavior.

In this note we shall consider a different effect. We shall assume that the proportion of individuals exhibiting the two behaviors, R_1 and R_2, is the same everywhere in the region occupied by the social group. We shall, however, introduce the effect of limitations of transmission of information.

It must be emphasized from the outset that all the following conclusions apply only to the case of transmission of information through social channels of the kind discussed previously (Rashevsky, 1950b; 1951b). Present day mass communication techniques invalidate those conclusions. For the study of some past social conditions these conclusions may, however, be of interest.

In preceding papers (Rashevsky, 1950b; 1951b) we have seen that the amount of information transmitted through a chain of individuals tends to zero as the length of the chain increases. The expression for that decrease is rather complicated and is given by a combination of exponentials. We also have considered the effect of the circumstance that in general there is a very large number of chains between any two individuals [Rashevsky, 1950b, equation (62)].

We shall now remark, that while the above-mentioned expression (62) gives us the maximum *possible* information that can be transmitted between two individuals regardless of time, the actual information which an individual can receive from another within a fixed time is much less. It takes a finite time to receive any signal from an immediate neighbor, and the number of neighbors which an individual is able to contact within a definite time is limited. Therefore, only relatively few channels, all in the neighborhood of the shortest one, actually will be used. The decrease of information with distance will therefore be given, with a sufficient approximation, by expression (58) of a previous paper (Rashevsky, 1950b).

Let us, for simplicity, assume that we may approximate the expressions for the decrease of information transmitted through a chain consisting of n individuals by a simple exponential:

$$R(n) = e^{-kn}. \tag{3}$$

If r is the length of the chain, and a the average distance between two neighbors, then

$$r = an\,. \tag{4}$$

If δ is the density of population, then we have approximately:

$$a = \frac{1}{\sqrt{\delta}}. \tag{5}$$

Hence, now expressing R as a function of r, we find from (3), (4), and (5):

$$R(x) = e^{-k\sqrt{\delta}\,r}. \tag{6}$$

Let an individual be at the origin of polar coordinates r,θ. The amount of information which the individual receives about all individuals located within the element of area $rdrd\theta$ is

$$\delta r e^{-k\sqrt{\delta}\,r} dr d\theta\,. \tag{7}$$

To obtain all the information which the individual receives about all individuals of the society, we must integrate expression (7) over the whole region occupied by the society. The result will depend in general on the size and shape of the region. Let us now find the amount T of information received by the individual about all individuals within a circle of radius r_0 which is much less than the linear dimension of the area occupied. It is given by the expression

$$T = 2\pi\delta \int_0^{r_0} r e^{-k\sqrt{\delta}\,r} dr$$

$$= 2\pi\delta \left[\frac{1}{k^2\delta} - \frac{1}{k\sqrt{\delta}} \left(r_0 + \frac{1}{k\sqrt{\delta}} \right) e^{-k\sqrt{\delta}\,r_0} \right]. \tag{8}$$

From the discussion in a preceding paper (Rashevsky, 1950b) it follows that the constant k is most likely to be of the order of unity. Namely, P' is of the order of 1 unless we have individuals strongly addicted to making errors, and $P'' << P'$. Hence $A \lesssim 1$. Therefore $A^n = e^{n \log A}$. Hence

$$k \sim \log A \lesssim 1.$$

With δ of the order of 10 ind/km², the exponential will be very small for values of $r_0 > 2$ km. Thus for circles with a radius of over 2 km, the expression (8) will already have practically reached the value $2\pi/k^2$, toward which it tends asymptotically as r_0 tends to infinity. We therefore see that for any area, the linear dimensions of which are much larger than 2 km, the information received by an individual about all the other individuals is a constant, independent of either N_0 or δ. The information per individual equals $2\pi/k^2N_0$, and decreases with N_0.

This result holds only to the extent to which $R(n)$ may be approximated by a simple exponential. Since it actually is a more complicated function, T in general, will depend on δ, and through it, indirectly on N_0.

The following consideration can be applied to any function $R(r)$, which decreases sufficiently rapidly, so that

$$\int_0^\infty rR(r)\,dr$$

is finite. Let us use as a measure of distance between two individuals the number n of individuals in the straight line between them. Then we can define a circle of radius n_0, such that the contribution to T coming from within the circle is, say, 99% of the total T, coming from the whole populated area. The quantity n_0 depends only on the psychophysiological characteristics of the individuals, and not on N_0 or on the size of the total area. In terms of the actual distance the radius of the circle is, according to expressions (4) and (5):

$$r_0 = \frac{n_0}{\sqrt{\delta}}. \tag{9}$$

The area of the circle is $\pi n_0^2/\delta$, and the number of individuals within it is πn_0^2. Regardless of N_0 and the size of the total populated area, 99% of the information which an individual has about all other individuals is confined to those πn_0^2 individuals.

Thus, regardless of the actual N_0, the number of individuals which a given individual can imitate is, with great approximation, πn_0^2, and is in principle expressible in terms of the parameters A and B, and, therefore, in terms of P' and P'' of the previous paper (Rashevsky, 1950b). This quantity should be substituted for N_0 in all the equations of the theory of imitative behavior, whenever N_0 becomes very large. As long as n_0 is not expressed explicitly in terms of P' and P'' and its numerical value computed, it is simpler to absorb that constant with the constant A of equation (1). For the study of equilibrium configurations which are determined by the equation

$$a\psi = A(X - Y), \tag{10}$$

we may put $a_1 = a/A$, and write

$$a_1\psi = X - Y. \tag{11}$$

The quantities X and Y now represent those *fractions* of the total number of individuals which exhibit behavior R_1 and R_2 respectively. We now have $X + Y = 1$.

LITERATURE

Rashevsky 1950a. "Mathematical Biology of Social Behavior: IV. Imitation Effects as a Function of Distance." *Bull. Math. Biophysics*, 12, 177–85.

——— 1950b. "Some Bio-Sociological Aspects of the Mathematical Theory of Communication." *Ibid.*, 12, 359–78.

——— 1951a. *Mathematical Biology of Social Behavior.* Chicago: University of Chicago Press.

——— 1951b. "A Note on the Theory of Communication through Social Channels." *Bull. Math. Biophysics*, 13, 139–46.

BULLETIN OF
MATHEMATICAL BIOPHYSICS
VOLUME 13, 1951

A SUGGESTED CHAIN PROCESS FOR RADIATION DAMAGE

A. T. REID AND H. G. LANDAU
COMMITTEE ON MATHEMATICAL BIOLOGY
THE UNIVERSITY OF CHICAGO

It has been suggested that when an organism is exposed to ionizing radiation the initial damage results from the occurrence of ionization in a so-called sensitive volume due to absorption of radiation quanta. The initial radiation damage is then transmitted or amplified to a level of macroscopic perception. In this paper a mechanism by which this transmission may take place and a finite Markov chain model applicable to this transmission are postulated and discussed.

This mechanism is assumed to be the depolymerization of essential chain molecules which are connected to some "central group" associated with the sensitive volume. The depolymerization of the macromolecules following a hit in the sensitive volume is postulated to be determined by a chain mechanism, which acts in a manner inverse to the mechanism controlling the polymerization process. A mathematical study of this problem is made using the theory of Markov chains. The probability of complete degradation of the chain macromolecule, and the probability of recombination of the units to give the intact chain were determined, assuming that the probabilty of successive steps in the degradation increase linearly from the intact state to that of complete breakdown.

1. *Introduction.* The idea of chain processes for the study of radio-biological phenomena has been suggested by F. Dessauer (1923) and developed by M. Blau and K. Altenburger (1923). The recent studies of I. Opatowski (1945; 1946 a, b) resulted in the development of a general theory of chain processes and their application to injury and recovery in biological systems following irradiation. In Opatowski's theory the occurrence of an effective event in the sensitive volume is considered as a transition of that volume to a new state. The observed effect is reached after a certain number of transitions between the states have taken place, so as to reach some final state which represents the observed effect.

It has been pointed out by J. Reboul (1942) that there is a difference between the probability that a hit occurs, and the probability that this hit will cause a certain effect. The importance of this concept has been discussed by J. Th. van der Werff (1948). The first probability depends on the geometry of the target and the absorption of radiation quanta, while the second probability is an expression of the degree of amplification or transmission of the initial hit damage through the system. This paper will be concerned with the second probability. A mathematical model, based on the theory of Markov chains, and a mechanism by which this transmission may take place will be postulated and discussed.

2. *Mechanism for the transmission of radiation damage.* In order to make our mathematical model structurally meaningful we will first consider the proposed mechanism. Consider the sensitive volume of an organism to be associated with some control molecule, or group of molecules, that was present in the early stages of development. If we assume free valances on this structure, the presence of which permits the addition of other cellular constituents, we can postulate the polymerization of essential long-chain molecules connected to this group. The long-chain molecules may be nucleic acids, etc.

The decomposition of these macromolecules following a hit in the sensitive volume is now postulated to be determined by a chain mechanism, which acts in a manner inverse to the mechanism controlling the polymerization process. Such a mechanism has been considered by W. Chalmers (1934) in his studies on addition polymers. The random degradation of high polymers has been studied by many authors (cf. Mark and Tobolsky, 1950), and the statistics and kinetics of this type of degradation are well-known. We cannot, however, use a random model to explain transmission for it is based on the probability of a break occurring at any link in the polymer chain. We are interested in the case where the initial break occurs at the end of the chain (i.e., the end connected to the control group), the subsequent steps in the degradation being the breaking off of successive monomer units from the damaged end. A random model might be applicable to a group of chain molecules with a number of control centers, and so spatially oriented that a hit in any one of these centers would result in the same effect.

3. *The mathematical model.* We consider a Markov chain (Feller, 1950) with finitely many states:

$$E_0 \rightarrow E_1 \rightarrow E_2 \rightarrow \cdots\cdot \rightarrow E_{a-1} \rightarrow E_a .$$

The system can be considered in the state E_0 initially (i.e., the chain is intact), and following a hit in the sensitive volume passes to the state E_1. The transition $E_0 \rightarrow E_1$ can be considered as a manifestation of the primary damage to the system, that is, the absorption of radiation quanta in the sensitive volume. The transitions $E_1 \rightarrow E_2 \rightarrow \cdots\cdot \rightarrow E_a$ will represent the transmission or amplification, and E_a will represent the state when the radiation damage becomes observable.

The transition probabilities, p_{jk} $(j,k = 0, 1, \cdots, a)$ are the conditional probabilities of the system in a state E_j passing to a state E_k. We define our transition probabilities as follows:

$$p_{j,j+1} = j/a\,, \quad (j = 1, \cdots, a-1), \tag{1}$$

$$p_{j,j-1} = 1 - j/a, \quad (j = 1, \cdots, a-1), \tag{2}$$

$$p_{00} = p_{aa} = 1\,, \tag{3}$$

$$p_{jk} = 0\,, \text{ otherwise.} \tag{4}$$

The forward one-step transitions (1) represent the transmission, and the reverse one-step transitions (2) represent recovery. Transmission of damage or recovery can occur only by passage from a state to its immediate neighbor. The condition that $p_{jj} = 1$ when $j = 0$ and a means that no change will occur after the states E_0 or E_a are reached; i.e., they are absorbing states, or, in the terminology of random-walk, there are absorbing barriers at $j = 0,a$. This means that no recovery is permitted from the state E_a should the system enter that state. If the system never enters E_a it must eventually return to E_0 (i.e., complete recovery, recombination of the units of the chain molecule) since the probability of remaining in any intermediate state $(E_1, \cdots, E_{a-1})$ is taken to be zero. The alternative to never reaching either E_0 or E_a would be for the system to shift from one to another of the intermediate states indefinitely. From the calculation below, it follows that there is zero probability for this indefinite transition between intermediate states.

We see from our definitions that the probability of the system reaching E_a increases as it moves away from the intact state, while the probability of recovery decreases. The assumption of linear increase in the transition probabilities represents, of course, an approximation for the sake of simplicity, made in the absence of more detailed information on the dependence of these probabilities on the extent of the degradation. Similar unsymmetric random-walk models have been studied by P. Ehrenfest and T. Ehrenfest (1907), M. C. Wang and G. E. Uhlenbeck (1945), and M. Kac (1947) in connection with the theory of Brownian motion.

We arrange our transition probabilities in a matrix $P = (p_{jk})$ where the first subscript stands for the row, the second for the column. A matrix P is called stochastic if $p_{jk} \geqslant 0$ and for every j,

$$\sum_{k=0}^{a} p_{jk} = 1\,.$$

We see from our definition of the transition probabilities that our matrix satisfies these conditions. The matrix P is given by

$$\begin{Vmatrix}
1 & 0 & 0 & 0 & 0 & 0 & \cdot\ \cdot & 0 & 0 & 0 \\
1-a^{-1} & 0 & a^{-1} & 0 & 0 & 0 & \cdot\ \cdot & 0 & 0 & 0 \\
0 & 1-2a^{-1} & 0 & 2a^{-1} & 0 & 0 & \cdot\ \cdot & 0 & 0 & 0 \\
0 & 0 & 1-3a^{-1} & 0 & 3a^{-1} & 0 & \cdot\ \cdot & 0 & 0 & 0 \\
0 & 0 & 0 & 1-4a^{-1} & 0 & 4a^{-1} & \cdot\ \cdot & 0 & 0 & 0 \\
\cdot & \cdot & \cdot & \cdot & \cdot & \cdot & \cdot\ \cdot & \cdot & \cdot & \cdot \\
\cdot & \cdot & \cdot & \cdot & \cdot & \cdot & \cdot\ \cdot & \cdot & \cdot & \cdot \\
0 & 0 & 0 & 0 & 0 & 0 & \cdot\ \cdot & a^{-1} & 0 & 1-a^{-1} \\
0 & 0 & 0 & 0 & 0 & 0 & \cdot\ \cdot & 0 & 0 & 1
\end{Vmatrix} .$$

3a. We wish to determine the probability λ_a, probability of observable damage, that the system initially in E_1 will eventually pass to E_a, also the probability λ_0, probability of recovery, that it will return to E_0. Now the system can arrive at E_a from E_1 only by first reaching E_{a-1} and then making the transition $E_{a-1} \rightarrow E_a$. The probability of the transition from E_1 to E_{a-1} in n steps will, as usual, be denoted by $p_{1,a-1}{}^{(n)}$. Then

$$\lambda_a = p_{a-1,a} \sum_{n=0}^{\infty} p_{1,a-1}{}^{(n)}, \tag{5}$$

where we use the natural definition, $p_{1,a-1}{}^{(0)} = 0$. Similarly, the probability λ_0 will be given by the sum of the probabilities that in n steps the system arrived in the state E_1, multiplied by the probability of transition, $E_1 \rightarrow E_0$. Hence

$$\lambda_0 = p_{10} \sum_{n=0}^{\infty} p_{11}{}^{(n)}, \tag{6}$$

where, of course, $p_{11}{}^{(0)} = 1$.

We see from our matrix P that $p_{11}{}^{(n)}$ is the element in the second row and second column of the nth power of P, that is, P^n; and $p_{1,a-1}{}^{(n)}$ is the element in the second row and $(a-1)$st column of P^n. Therefore

$$\sum_{n=0}^{N} p_{11}{}^{(n)}$$

is the element in the second row and second column of $I + P + P^2 + \cdots + P^N$, where I is the unit matrix. This sum does not converge for $N \rightarrow \infty$, but we can compute the sums in (5) and (6) as follows.

The matrix P can be written in the form of a partitioned matrix

$$\left\|\begin{array}{c|c|c} 1 & 0 & 0 \\ \hline A & B & C \\ \hline 0 & 0 & 1 \end{array}\right\|$$

where

$$B=\begin{Vmatrix} 0 & a^{-1} & 0 & 0 & \cdots & 0 & 0 \\ 1-2a^{-1} & 0 & 2a^{-1} & 0 & \cdots & 0 & 0 \\ 0 & 1-3a^{-1} & 0 & 3a^{-1} & \cdots & 0 & 0 \\ \cdot & \cdot & \cdot & \cdot & \cdots & \cdot & \cdot \\ \cdot & \cdot & \cdot & \cdot & \cdots & \cdot & \cdot \\ \cdot & \cdot & \cdot & \cdot & \cdots & \cdot & \cdot \\ 0 & 0 & 0 & 0 & \cdots & 0 & 1-2a^{-1} \\ 0 & 0 & 0 & 0 & \cdots & a^{-1} & 0 \end{Vmatrix}. \tag{7}$$

That is, B is the reduced matrix obtained from P by eliminating the first and last rows and columns. Now it is clear that P^n has the form

$$\left\|\begin{array}{c|c|c} 1 & 0 & 0 \\ \hline A_n & B^n & C_n \\ \hline 0 & 0 & 1 \end{array}\right\| ;$$

where B^n is the nth power of B.

Putting

$$e_{11}=\sum_{n=0}^{\infty} p_{11}{}^{(n)}, \tag{8}$$

we have e_{11} equal to the element in the first row and first column of

$$\sum_{n=0}^{\infty} B^n,$$

provided this series converges. The convergence, and the limit, may be obtained as follows. Let

$$S_N=\sum_{n=0}^{N} B^n, \tag{9}$$

then

$$S_N-S_NB=I-B^{N+1}. \tag{10}$$

We show that $\lim_{N\to\infty} B^{N+1}=0$. The elements of B^{N+1} are p_{jk}, for $j, k=1, 2, \cdots, a-1$, and they are all positive. We use induction to show that

$$\sum_{j=1}^{a-1} p_{jk}^{(N+1)} \leqq (1-2a^{-1})^{N+1}.$$

From the definition of B,

$$\sum_{j=1}^{a-1} p_{jk} = \sum_{j=1}^{a-1} p_{jk}^{(1)} = 1-2a^{-1}.$$

Using the induction hypothesis,

$$\sum_{j=1}^{a-1} p_{jk}^{(N)} \leqq (1-2a^{-1})^{N},$$

we have

$$\sum_{j=1}^{a-1} p_{jk}^{(N+1)} = \sum_{j=1}^{a-1} \sum_{\beta=1}^{a-1} p_{j\beta}^{(N)} p_{\beta k} = \sum_{\beta=1}^{a-1} p_{\beta k} \sum_{j=1}^{a-1} p_{j\beta}^{(N)}$$

$$\leqq (1-2a^{-1})^{N} \sum_{\beta=1}^{a-1} p_{\beta k} \leqq (1-2a^{-1})^{N+1}.$$

Hence $p_{jk}^{(N+1)} \leqq (1-2a^{-1})^{N+1}$ and $p_{jk}^{(N+1)} \to 0$ for $N \to \infty$, since $1-2a^{-1} < 1$.

Then from (10),

$$\lim_{N\to\infty} S_N = (I-B)^{-1}, \tag{11}$$

provided $(I-B)$ is non-singular, which we now show by calculating its determinant.

We have

$$I-B = \begin{Vmatrix} 1 & -a^{-1} & 0 & \cdot & \cdot & \cdot & \cdot \\ -1+2a^{-1} & 1 & -2a^{-1} & \cdot & \cdot & \cdot & \cdot \\ 0 & -1+3a^{-1} & 1 & \cdot & \cdot & \cdot & \cdot \\ \cdot & \cdot & \cdot & \cdot & \cdot & \cdot & \cdot \\ \cdot & \cdot & \cdot & \cdot & \cdot & 1 & -1+2a^{-1} \\ \cdot & \cdot & \cdot & \cdot & \cdot & a^{-1} & 1 \end{Vmatrix} \tag{12}$$

$$= a^{-(a-1)} \begin{Vmatrix} a & -1 & 0 & \cdot & \cdot & \cdot \\ -a+2 & a & -2 & \cdot & \cdot & \cdot \\ 0 & -a+3 & a & \cdot & \cdot & \cdot \\ \cdot & \cdot & \cdot & \cdot & \cdot & \cdot \\ \cdot & \cdot & \cdot & \cdot & a & -a+2 \\ \cdot & \cdot & \cdot & \cdot & -1 & a \end{Vmatrix}.$$

Let Δ be the determinant of this matrix, so $|I-B| = a^{-(a-1)}\Delta$. To compute Δ we add the elements in each row and place these sums in

the first column, then add the elements in each row excluding the first column and put these in the second column, etc.
Then

$$\Delta = \begin{vmatrix} a-1 & -1 & 0 & 0 & \cdot & 0 & 0 \\ 0 & a-2 & -2 & 0 & \cdot & 0 & 0 \\ 0 & 0 & a-3 & -3 & \cdot & 0 & 0 \\ 0 & 0 & 0 & a-4 & \cdot & 0 & 0 \\ \cdot & \cdot & \cdot & \cdot & \cdot & \cdot & \cdot \\ 0 & 0 & 0 & 0 & \cdot & 2 & -a+2 \\ a-1 & a-1 & a-1 & a-1 & \cdot & a-1 & a \end{vmatrix} . \tag{13}$$

Expanding by elements of the first row

$$\Delta = (a-1) \begin{vmatrix} a-2 & -2 & 0 & \cdot & 0 & 0 \\ 0 & a-3 & -3 & \cdot & 0 & 0 \\ 0 & 0 & a-4 & \cdot & 0 & 0 \\ \cdot & \cdot & \cdot & \cdot & \cdot & \cdot \\ 0 & 0 & 0 & \cdot & 2 & a-2 \\ a-1 & a-1 & a-1 & \cdot & a-1 & a \end{vmatrix} + (a-1)\,! . \tag{14}$$

Continuing to expand by elements of the first row gives

$$\Delta = (a-1)(a-2) \times \begin{vmatrix} a-3 & -3 & \cdot & 0 & 0 \\ 0 & a-4 & \cdot & 0 & 0 \\ \cdot & \cdot & \cdot & \cdot & \cdot \\ 0 & 0 & \cdot & 2 & -a+2 \\ a-1 & a-1 & \cdot & a-1 & a \end{vmatrix} + (a-1)\,!\left[1 + \frac{a-1}{1}\right]$$

$$= \frac{(a-1)\,!}{2!} \begin{vmatrix} 2 & -a+2 \\ a-1 & a \end{vmatrix} \tag{15}$$

$$+ (a-1)\,!\left[1 + \binom{a-1}{1} + \binom{a-1}{2} + \cdots\cdot + \binom{a-1}{a-4}\right]$$

$$= (a-1)\,!\left[1 + \binom{a-1}{1} + \cdots\cdot + \binom{a-1}{a-3} + a\right]$$

$$= (a-1)\,!\sum_{k=0}^{a-1}\binom{a-1}{k} = 2^{a-1}(a-1)\,!.$$

The cofactor of the element in the first row and first column of Δ is equal to

$$\frac{\Delta-(a-1)!}{a-1}=(a-2)!\,(2^{a-1}-1).$$

Therefore

$$e_{11}=a\left[\frac{(a-2)!\,(2^{a-1}-1)}{(a-1)!\,2^{a-1}}\right]=\frac{a}{a-1}\left(1-\frac{1}{2^{a-1}}\right). \tag{16}$$

We find therefore that

$$\lambda_0=(1-a^{-1})\,e_{11}=1-\frac{1}{2^{a-1}}. \tag{17}$$

Similarly we obtain

$$\lambda_a=\frac{1}{2^{a-1}}, \tag{18}$$

so that $\lambda_0+\lambda_a=1$ as remarked above.

3b. An alternate procedure, which also enables us to obtain the probability λ_a is as follows. Let x_k be the probability of being absorbed at E_a starting from the state E_k; we have then the difference equation

$$\begin{aligned} x_k&=\frac{k}{a}x_{k+1}+\left(1-\frac{k}{a}\right)x_{k-1}=\frac{k+1}{a}x_{k+1}\\ &-\frac{1}{a}x_{k+1}+\left(1-\frac{k-1}{a}\right)x_{k-1}-\frac{1}{a}x_{k-1}. \end{aligned} \tag{19}$$

This equation is valid for $1\leqq k\leqq a-1$, and valid for all $k\geqq 1$ if we define $x_{a+1}=1$. We have also the boundary conditions

$$x_0=0\,,\; x_a=1\,. \tag{20}$$

Let

$$f(z)=\sum_{k=0}^{\infty}x_k z^k\,,\; |z|\leqq 1\,.$$

Then we can rewrite (19) as

$$\begin{aligned} \sum_{k=0}^{\infty}x_k z^k&=\sum_{k=0}^{\infty}\frac{k}{a}x_k z^{k-1}-\frac{1}{a}\sum_{k=0}^{\infty}x_k z^{k-1}\\ &+\left(1-\frac{1}{a}\right)\sum_{k=0}^{\infty}x_k z^{k+1}-\sum_{k=0}^{\infty}\frac{k}{a}x_k z^{k+1}; \end{aligned} \tag{21}$$

and, using

$$f'(z) = \sum_{k=0}^{\infty} k x_k z^{k-1},$$

we obtain

$$f'(z) + \frac{\left\{(a-1)z - \dfrac{1}{z} - a\right\}}{1-z^2} f(z) = 0. \tag{22}$$

The solution of (22) is readily obtained since the equation can be written

$$\frac{f'(z)}{f(z)} = \frac{1}{z} + \frac{1}{1-z} + \frac{a-1}{1+z},$$

so that

$$f(z) = C\frac{z(1+z)^{a-1}}{1-z} = Cz\left[\sum_{k=0}^{a-1}\binom{a-1}{k} z^k\right]\left[\sum_{n=0}^{\infty} z^n\right], \tag{23}$$

where C is a constant of integration. We are only interested in the coefficients x_k, $(0 \leqq k \leqq a)$. These can be seen to be

$$x_k = C\sum_{m=0}^{k-1}\binom{a-1}{m}. \tag{24}$$

Utilizing the boundary conditions (20) to determine the constant C, we find that

$$1 = C\left[\binom{a-1}{0} + \binom{a-1}{1} + \cdots + \binom{a-1}{a-1}\right] = 2^{a-1}C,$$

so that

$$x_k = \sum_{m=0}^{k-1}\binom{a-1}{m} \Big/ 2^{a-1},\ 0 \leqq k \leqq a. \tag{25}$$

If we let $k = 1$ in (25), we find that

$$x_1 = \binom{a-1}{0} \Big/ 2^{a-1} = \frac{1}{2^{a-1}}, \tag{26}$$

since $\binom{a-1}{0} = 1$. Hence x_1 is equal to λ_a determined previously.

4. *Concluding remarks.* In this paper we have discussed the transmission of radiation damage under the assumption that a hit in the sensitive volume of an organism is followed by a chain depolymerization of some essential macromolecules. We also assumed that these macromolecules have their origin at some structure which is present in the early stages of cell development. The results obtained, (17) and (18), show that for large values of a recovery is almost certain. In terms of biological systems this means that the probability of an observed effect and the probability of recovery are related to the extent of polymerization of the macromolecules, when radiation quanta are absorbed in the sensitive volume; the probability of an observed effect being greater during the initial stages of the polymerization process. From studies on the sensitivity of organisms to irradiation (Sax and Swanson, 1941) it has been shown that sensitivity changes with age. The model postulated here is based on the assumption that the sensitive volume is a dynamic cellular entity; therefore we would expect its properties to be intimately related to the metabolic and physicochemical activities of the cell.

It has been pointed out that many organisms are highly sensitive to radiation during the metaphase of the mitotic process. Since aster formation occurs during the metaphase we might speculate on a relationship between the site of aster formation and the sensitive volume. The possible influence of X-ray irradiation on aster formation has, apparently, not been investigated. In terms of our model the centrosome might be considered as the control group, and the asters the chain molecules that undergo depolymerization.

This work was aided in part by a grant from the Dr. Wallace C. and Clara A. Abbott Memorial Fund of The University of Chicago.

LITERATURE

Blau, M. and K. Altenburger. 1923. "Über einige Wirkungen von Strahlen." *Zeit. f. Physik*, 12, 315–29.

Chalmers, W. 1934. "The Mechanism of Macropolymerization Reactions." *Jour. Amer. Chem. Soc.*, 56, 912–22.

Dessauer, F. 1923. "Über einige Wirkungen von Strahlen." *Zeit. f. Physik*, 12. 38–47.

Ehrenfest, P. and T. Ehrenfest. 1907. "Uber zwei bekannte Einwände gegen das Boltzmannsche H - theorem." *Phys. Zeits.*, 8, 311–14.

Feller, W. 1950. *An Introduction to Probability Theory and its Applications.* New York: John Wiley and Sons, Inc.

Kac, M. 1947. "Random Walk and the Theory of Brownian Motion." *Amer. Math. Month.*, 54, 369–91.

Mark, H. and A. V. Tobolsky. 1950. *Physical Chemistry of High Polymeric Systems.* New York: Interscience Publishers, Inc.

Opatowski, I. 1945. "Chain Processes and Their Biophysical Applications: I. General Theory." *Bull. Math. Biophysics*, 7, 161–80.

———. 1946a. "Chain Processes and their Biophysical Applications: II. The Effect of Recovery." *Ibid.*, 8, 7–15.

———. 1946b. "The Probabilistic Approach to the Effects of Radiation and Variability and Sensitivity." *Ibid.*, 8, 101–19.

Reboul, J. 1942. *Les Bases Physiques et Biologiques de la Roentgentherapie.* (Ed. P. Lamarque.) Paris: Masson et Cie.

Sax, K, and C. P. Swanson. 1941. "Differential Sensitivity of Cells to X-rays." *Amer. Jour. Botany*, 28, 52–9.

Wang, M. C. and G. E. Uhlenbeck. 1945. "On the Theory of the Brownian Motion. II." *Revs. Mod. Physics*, 17, 323–42.

van der Werff, J. Th. 1948. *Biological Reactions Caused by Electric Currents and by X-rays.* New York: Elsevier Publishing Co., Inc.

BULLETIN OF
MATHEMATICAL BIOPHYSICS
VOLUME 13, 1951

APPLICATIONS OF MATRIX ALGEBRA TO COMMUNICATION NETS

Alfonso Shimbel
Committee on Mathematical Biology
The University of Chicago

A "generic" problem amenable to matrix algebraic treatment is outlined. Several examples are given and one, a communication system, is studied in some detail.

A typical structure matrix is used to describe the channels of communication and a "status" matrix is used to describe the distribution of information in the system at any time.

A theorem is proved relating the status matrix at any time t to the tth power of the structure matrix.

The elements of the communication system are interpreted as individuals who can send messages to each other. For the individuals attempting to solve a "group problem" certain relations are derived between the structure and status matrices and time of solution.

The structure of the communication system is permitted to vary with time. A general theorem is proved relating the status matrix to the matrix product of the series of structure matrices representing the changing structure of the system.

Some suggestions are made for further generalizations. In particular, it is suggested that so-called "higher order" information transmission can be similarly treated.

Introduction. A variety of problems which have been (or could be) studied by the use of matrix representations have some interesting properties in common. The kinds of problems which we refer to are exemplified by: the mathematics of radiation and cosmic ray counters, the theory of neutron production and absorption, mathematical genetics, experimental design, the mathematics of peck right, epidemiology, the ontogeny of neural nets, stereochemistry, communication systems, and a host of others.

This wide range of problems (or significant aspects of them) may be regarded as special cases of the following "generic" problem:

A certain number (n) of essentially "equivalent" objects are the elements of a system. Associated with every *ordered pair* of elements (which may be regarded as distinguishable) is the *affirmation or negation* of k relations. We may symbolize the affirmation of the pth relation between the ith and jth elements by the expression iR_pj. This, of course, need not imply that jR_pi, that is, the relation R_p need not be symmetric.

The negation of the pth relation between the ith and jth elements may be written as $iR_p^{-1}j$.

In addition to the *relations* associated with the ordered pairs of the system each *element* may be associated with one or more of m *intrinsic* properties. Thus the affirmation (of possession) of intrinsic property q by element i can be symbolized by the expression iP_q, and its negation by iP_q^{-1}.

The relations and intrinsic properties of the system may, in general, imply a dynamics which is reflected by a quantized temporal shift of relational and intrinsic property *affirmations* to *negations* or vice versa.

Matrix Representation. For any given problem of this kind our attention may be focused upon the "structures" implied by the relations between the elements or upon the dynamics of the system. In either case matrix representation can be used to advantage. Such a system can be described by matrices in the following way:

First, number the elements of the system from one to n in some arbitrary fashion. Assume for illustration that only one type of relation will be considered. In other words, for each ordered pair of elements i,j we will say either iRj or $iR^{-1}j$, i.e., i is related to j, or i is not related to j.

The set of all such relations can be conveniently described by an $n \times n$ matrix whose elements are either R or R^{-1}. Thus if a typical element of the matrix e_{ij} is R, then we will say iRj. If, however, the typical matrix element e_{ij} is R^{-1}, then we will say $iR^{-1}j$. Such a matrix can be called a *structure* matrix insofar as the relations between the elements imply a structure of the system. The matrix representation can be extended to include any number, say k, of different kinds of relations. In this case it would be necessary to use an $nk \times n$ matrix or $kn \times n$ matrices to represent the totality of relationships.

In a similar way the distribution of intrinsic properties among the elements of the system can also be represented by a matrix. If we consider a system possessing m different classes of intrinsic properties, then an $n \times m$ matrix will do the job. Such a matrix can be called a *status* matrix insofar as the distribution of properties among the elements of the system describes a status of the elements as compared to each other.

An Example. For the sake of illustration, consider the following problem. *How many structurally different compounds are represented by the formula* $C_\mu H_\nu$ (only saturated hydrocarbons considered)?

If we picture such a compound in a conventional steric diagram, it becomes evident that every carbon atom in the molecule (except for the special case of methane) *is chemically bound to* one or more other carbon atoms. In the most general case such bonds may be single, double, or triple, but for saturated compounds only single bonds occur.

Now, if we let the integer 1 represent the relation *"has a single bond with"* and if we let 0 represent its negation, that is, *"is not bound to,"* then, by arbitrarily numbering the carbon atoms from 1 to μ we can write a series of propositions of the form $i1j$ and $p0q$. In words, these expressions mean "carbon atom i *has a single bond with* carbon atom j" and "carbon atom p *is not bound to* carbon atom q."

According to the procedure outlined above, the totality of relations among the carbon atoms can be represented by a $\mu \times \mu$ *structure* matrix.

For the trivial case of CH_4 (methane) we have a 1×1 matrix whose only element is 0. In other words, the only carbon atom in the molecule has no bonds with itself. Ethane (C_2H_6) is represented by the 2×2 *structure* matrix

$$\begin{pmatrix} 0 & 1 \\ 1 & 0 \end{pmatrix}.$$

The elements of the major diagonal of such a structure matrix will always be 0 since the statement "atom i has a single bond with atom i" is meaningless. The relation "has a single bond with" as used here is always reciprocal, so it follows that the structure matrix will always be symmetric around the major diagonal. Also note that the sum of the elements of the structure matrix is exactly twice the number of carbon atoms used in forming the "backbone" of the molecule. It follows then that

$$4\mu - 1/2 \sum_{j=1}^{\mu} \sum_{j=1}^{\mu} e_{ij} = \nu . \qquad (1)$$

The class of all pure saturated hydrocarbons having the formula $C_\mu H_\nu$ can, therefore, be represented by a class of $\mu \times \mu$ matrices. It must be noted, however, that the total number of isomers of the form $C_\mu H_\nu$ is considerably smaller than the number of different $\mu \times \mu$ matrices which can be used to represent them. This is due to the fact that the numbering of the carbon atoms is arbitrary and that renumbering does not change the structure. It is further complicated by the fact that renumbering also may leave the matrix unchanged.

For these reasons many matrices are equivalent in the sense that they represent the same substance. The original problem, therefore, of finding the number of different substances represented by the formula $C_\mu H_\nu$ reduces to the problem of *counting the number of subclasses of equivalent matrices making up the class of* $\mu \times \mu$ *matrices representing the formula* $C_\mu H_\nu$.

The fact is that this particular problem has been attacked and partially solved by number and group theoretical methods (Polya, 1936). These results are, of course, translatable into the language of matrices and, therefore, should have a direct bearing on all of the other phenomena subsumed by the aforementioned "generic" problem.

Other Examples. In the above example no *status* matrix is involved and the attention is focused on the *structure* of the system. However, as was mentioned in the introduction, the existence of a structure matrix and status matrix describing the same system frequently implies a dynamics. Accordingly, the dynamics of a neural net conforming to the postulates of McCulloch and Pitts has been described and analyzed by the use of matrix algebra (Landahl and Runge, 1946).

In this case the elements of the system are neurons. The *relations* appearing in the *structure* matrix are "can stimulate" and "can inhibit." The intrinsic properties associated with the status vector are "is active" and "is not active." In this paper it is shown that consecutive products of the status vector with the structure matrix give consecutive status vectors which represent the "state" of the net for different moments.

In a subsequent paper H. D. Landahl (1947) extends the results of the first paper and treats the "reverse problem," i.e., instead of describing the behavior of a given net he starts out with a given dynamics and defines the kind of net which will exhibit such behavior.

As a final example A. Rapoport (1949) and H. G. Landau (1950) use matrix theory in the study of the dynamics of chicken "societies" organized by the relation of "peck right."

The foregoing is not intended as a proof for the wide applicability of matrix representation, for this is well known. The point is that in the cases cited above the structure matrix represents, in one way or another, a connected system, a network, an organization, or "lacework" of simple relations. The structure matrix can, therefore, be interpreted as an important invariant of what may be loosely termed "group order." An extensive study of square matrices, therefore, with an eye to the structures they imply may lead to useful definitions of such vague concepts as organization, group stability, and so on.

Some important steps in this direction appear in recent literature (Luce and Perry, 1949; Luce, 1950). The authors define an organizational concept which they call a *clique* and the more general notion of an n-*clique*. Roughly speaking, a clique is a certain ordering of relations in a subgroup of a system. R. D. Luce and A. D. Perry show certain relations between the existence of cliques and certain properties of the matrices representing the system.

In addition, these authors apply matrix algebra to a simple "communication system" in a manner quite analogous to the Landahl-Runge treatment of neural nets. They arrive at a recursion formula for consecutive states of the system which is also analogous to the formula of Landahl and Runge.

Group Communication. The Problem. The following problem, although in a way more general than that approached by Landahl and Runge, Luce and Perry, is nevertheless treated in a similar manner. The statement of the problem and some of the definitions may, therefore, be expected to overlap somewhat.

Suppose that a group of n persons are asked to play the following game. Each member is told at the outset that he must send "messages" to certain other *specified* members of the group. On the other hand, he is not told who the recipients of the other members' "messages" are. In fact, at the beginning of the game he does not even know who, if anyone, will send messages to him. The point of the game is for each member to know the complete structure of their communication system. In other words, each member must know the destination of every other member's messages.

Accordingly, the messages themselves must contain such information. A typical message will read "The destination of C's messages is D, the destinations of B's messages are A and D, and so on." The expression "the destinations of B's messages are A and D" is actually a statement of all the information which member B possessed at the beginning of the game. Accordingly we shall refer to such expressions as *primary elements* of information.

Now since there are n members in the group, there must also be n primary elements of information. The game will end, therefore, when every member possesses n different primary elements of information.

The Method. If we number the members of the group from 1 to n in some arbitrary fashion we can proceed in the usual manner to construct a structure matrix which will represent the communication system. The matrix can be constructed by rows. To write down the jth row of the matrix we ask "Does member j send messages to member i"? If the answer is *yes,* then the element e_{ij} of the structure matrix is one. If the answer is *no,* then the element e_{ij} is zero. By repeating this procedure n^2 times the complete structure matrix can be written down.

For example, see the three member group diagrammed below in Figure 1 and a corresponding structure matrix as follows:

$$\begin{Bmatrix} 1 & 0 & 1 \\ 1 & 1 & 0 \\ 0 & 1 & 1 \end{Bmatrix} . \tag{2}$$

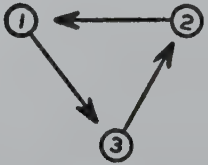

FIGURE 1

Notice that the diagonal elements of the structure matrix are all 1's. This would be as though each member of the group sends himself messages. This notation is useful in the operations which follow. We can think of it as though each number repeatedly "reminds himself of" or "remembers" the information which he has already obtained.

A status matrix describing the distribution of primary information throughout the group can also be constructed. This can be done columnwise. To write down the jth element of the ith column we must ask: "Does member i possess the primary element of information associated with member j"? If the answer is *yes,* then the jth element of the ith column is one. If the answer is *no,* then the jth member of the ith column is zero. This process defines the status matrix.

At the beginning of the game each member of the group will possess only the primary information associated with himself. In other words, all that he will know is where he sends his own messages. The status matrix at the beginning of the game will, therefore, be the identity matrix. The matrix will have 1's along the major diagonal and zeros everywhere else.

Successive States. As the game proceeds the information will begin to shuttle from person to person according to the pathways of the system. This will result in a constantly changing status matrix. Now, if the rate of flow of messages were in no way controlled, certain differences between the various people playing the game would begin to show themselves. Some members of the group may find themselves, for example, sending only one-third as many messages per unit time as other members. In order to remove such differences between the individuals from our considerations we will stipulate that each member must send messages along all of his permissible channels exactly once per unit time. The problem is now well defined and we can ask the first question, namely, "How long will the game last"?

Before going on to answer this question it should be noted that a slight change in the definition of the status matrix makes it possible for us to prove a useful theorem. To this end we will say that if the general element of the status matrix e_{ij} is some *positive integer,* then member i possesses the primary element of information associated with member j. However, as before, if e_{ij} is zero, then we shall say that the member i is ignorant of the primary element of information associated with member j.

Fundamental Theorem. The status matrix, *representing the distribution of primary elements of information among the members of the system after* t *units of time, is given by the* t*th power of the* structure matrix *in the sense of ordinary matrix multiplication.*

Proof: *Lemma.* If $\boldsymbol{S}$ denotes the structure matrix and $\boldsymbol{I}_t$ denotes the status matrix after t units of time then,

$$\boldsymbol{I}_{t+1} = \boldsymbol{I}_t \boldsymbol{S} . \tag{3}$$

Let $e_{ij}^{(t)}$ denote the typical element of the status matrix after t units of time. Also, let s_{ij} denote the typical element of the structure matrix. According to the definition of ordinary matrix multiplication, we have

$$p_{ij} = s_{i1}e_{1j}^{(t)} + s_{12}e_{2j}^{(t)} + \cdots\cdot + s_{in}e_{nj}^{(t)}, \tag{4}$$

where p_{ij} is the typical element of the matrix product $\boldsymbol{I}_t \boldsymbol{S}$.

Since none of the elements s_{ik} or $e_{kj}^{(t)}$ is ever negative, it follows that neither the right-hand member of expression (4) nor any of its terms $s_{ik}e_{kj}^{(t)}$ can ever be negative. This implies that if the right-hand member of expression (4) is zero then all of its terms

$s_{ik}e_{kj}^{(t)}$ are individually zero. However, $s_{ik}e_{kj}^{(t)} = 0$ means either $s_{ik} = 0$, $e_{kj}^{(t)} = 0$, or both. But, according to the definition of the structure matrix, $s_{ik} = 0$ tells us that member i never receives messages from member k . From the definition of the status matrix $e_{kj}^{(t)} = 0$ tells us that member k (at the time t) *does not* possess the primary element of information associated with member j . If *either* (or both) of these conditions hold, it follows that member i *could not* obtain the primary element of information associated with member j *at the time* $t + 1$ *from member* k . If this is true for *all of the terms* in the right-hand member of expression (4), then it follows that member i *could not* obtain the primary element of information associated with member j *at the time* $t + 1$ *from any other member.* We must conclude then that, given these conditions, the general element of the status matrix at the time $t + 1$ must be zero, i.e., $e_{ij}^{(t+1)} = 0$. But, given these conditions, we see from expression (4) that p_{ij} is zero. Hence, for this case we find that $p_{ij} = e_{ij}^{(t+1)}$.

The only remaining possibility is for the right-hand member of expression (4) to be a positive integer. This means that $s_{ik}e_{kj}^{(t)}$ (for at least one k) is a positive integer. In order for this to be true we must have $s_{ik} = 1$ and $e_{kj}^{(t)} = +$ integer. But $s_{ik} = 1$ means that member i *does* receive messages from member k . Also, $e_{kj}^{(t)} = +$ integer means that member k (at the time t) *does* possess the primary element of information associated with member j . From this we must conclude that member i , at the time $t + 1$, *will* possess the primary element of information associated with member j . This implies that $e_{ij}^{(t+1)}$ must be a positive integer. But under these conditions p_{ij} is a positive integer, as a glance at expression (4) will show. Hence again $e_{ij}^{(t+1)} = p_{ij}$. Thus the lemma is proved. In other words, expression (3) is a valid recursion formula.

Now let us recall that the status matrix $\boldsymbol{I}_0$ (at the beginning of the game) is simply the identity matrix. Using expression (3), we get $\boldsymbol{I}_1 = \boldsymbol{I}_0\boldsymbol{S}$. But $\boldsymbol{I}_0\boldsymbol{S} = \boldsymbol{S}$; hence $\boldsymbol{I}_1 = \boldsymbol{S}^1$. It follows by induction that the fundamental theorem is true, that is,

$$\boldsymbol{I}_t = \boldsymbol{S}^t . \qquad (5)$$

Expression (5) makes it possible for us to give at least a formal solution to the original problem, namely: "How long will the game last"?

If any element of the status matrix $\boldsymbol{I}_t$ is zero, then we know that at least one member of the group does not yet possess the primary information associated with at least one other member, and so the game is not finished. The game will end at the first moment when every element of the status matrix is non-zero. *The game will end, therefore after* T *units of time, where* T *is the smallest power of the structure matrix containing no zero elements.*

Adequate Systems. Not all groups will be able to end their game. Their channels of communication may be inadequate. Such inadequacy may be due to an insufficient number of channels or an inadequate arrangement of those which are available. We shall refer to the structure matrix of such an inadequate communication system as an *inadequate* matrix. Similarly, the structure matrix of an inadequate communication system can be called an *adequate* matrix. Some interesting details relating to these notions of adequate and inadequate matrices are developed by Luce (1950) in the section on *connectivity in a structure.*

In order for a structure to be adequate, it is *necessary* for every member to send messages to at least one other member and to receive messages from at least one other member. In fact, there must exist at least one path of channels from any given member of the group to every other member. If this were not so, that is, if no such path existed between member i and member j, for example, then the primary element of information associated with member i would never be available to member j. In terms of the structure matrix this means that there must exist some sequence of integers k_1, k_2, k_3, $\cdots\cdot$ k_m (not necessarily all different) such that s_{ik_1}, $s_{k_1k_2}$, $s_{k_2k_3}$ $\cdots\cdot$ s_{k_mj} are all 1's.

The Cycle. Since every member must send messages to at least one other member, it follows that *at least* n channels are *necessary* in order to construct an adequate system. In fact, this number is sufficient if the channels are laid out in a simple closed chain which includes all of the members of the group. We shall refer to the matrix of such a structure as a *minimal-cyclic* matrix.

Changing Structure. The game can be complicated somewhat by permitting the members to shift their channels of communication in some prescribed temporal order. The structure matrix, under these conditions, would change from time to time.

In order to describe such a system it would be necessary to write down a series of structure matrices $\boldsymbol{S}_1$, $\boldsymbol{S}_2$, $\cdots\cdot$, $\boldsymbol{S}_t$, $\cdots\cdot$, where $\boldsymbol{S}_t$ represents the particular communication structure being used at the time t. We shall refer to such a series of matrices as a ***structure series.***

The General Theorem. The status matrix, representing the dis-

tribution of primary information among the members of the system after t *units of time, is given by the matrix product* $S_1S_2S_3 \cdots S_t$, *in the sense of ordinary matrix multiplication.*

Proof: In proving recursion formula (3) we assumed that the structure matrix S was constant with time. But this assumption in no way affects the argument, since it deals only with the tth exchange of information. This permits us to write the slightly more general recursion formula:

$$I_{t+1} = I_t S_t\,. \tag{6}$$

But since $I_1 = I_0 S_1 = S_1$, the general theorem follows by a simple induction on expression (6).

Adequate Structure Series. We have already shown that certain trivial structure series (constant adequate structure) results in a finite game. We may now ask for more general conditions on the structure series such that it will be *adequate.*

Theorem. The maximum number of different structure matrices representing possible communication systems between n *labeled members is given by the expression* $2^{(n-1)n}$.

Proof: The 1's appearing in the ith row of a structure matrix tell us (by definition) to whom member i sends his messages. It may be that he sends no messages to anyone, in which case the only 1 appearing in the ith row would be element s_{ii}. But this can happen in only one way. It may be that member i *does* send messages to exactly one other member, in which case a 1 would appear elsewhere in the row. This could happen in $n-1$ different ways. In general, member i may send messages to k other members. This could happen in $\binom{n-1}{k}$ different ways, where $\binom{n-1}{k}$ is the number of ways in which we can choose k objects from $n-1$ objects, all different. The number of ways N in which a given row can be "disposed of" is given by the expression

$$N = 1 + (n-1) + \binom{n-1}{2} + \binom{n-1}{3} + \cdots + \binom{n-1}{n-1} = 2^{n-1}. \tag{7}$$

It follows that the number of ways in which all of the rows can be disposed of together is $N^n = 2^{(n-1)n}$, which proves the theorem.

Definition: Any structure series which indefinitely repeats a subseries of structure matrices will be called a *cyclic structure series.*

Theorem. Any cyclic structure series which contains one or more adequate matrices is an adequate structure series.

Proof: If a positive integer appears in some element of the status matrix at some time t, then, by virtue of the fact that each member "reminds himself of" his already acquired information (every diagonal element of any structure matrix is 1), that particular element of the status matrix can never again be zero, for any time after t. It follows that if a given adequate matrix is applied to the changing status matrix every k units of time, then every element of the status matrix will be a positive integer in at most kT units of time, where T is the minimum power of the adequate structure matrix containing no zeros. Such a cyclic structure series must, therefore, be adequate.

Since the game always ends at the moment when zeros no longer appear in the status matrix, it follows that the game will last T units of time, where T is the *minimum* subscript of the structure matrix for which the product $S_1S_2S_3 \cdots\cdot S_T$ contains no zeros. That this product contains no zeros for *some* T is, in fact, the definition of an adequate structure series.

It is possible for every matrix of a structure series to be inadequate and still form an adequate structure series. For example, consider the structure series $S_1S_2S_1S_2 \cdots\cdot$, where

$$S_1 = \begin{pmatrix} 1 & 0 \\ 1 & 1 \end{pmatrix} \text{ and } S_2 = \begin{pmatrix} 1 & 1 \\ 0 & 1 \end{pmatrix}.$$

It is readily seen that the element e_{21} of structure matrix S_1 and element e_{12} of structure matrix S_2 will remain zeros for all powers of these matrices. This means that both S_1 and S_2 are *inadequate* matrices. The product S_1S_2, however, contains no zeros; hence, the *structure series is adequate.*

Efficiency. For a group of any given size certain structure matrices or structure series end the game faster than others. The *solution time* T is, therefore, a kind of measure of the efficiency of the communication system. The various adequate structure matrices and series can, therefore, be ordered in a preferential hierarchy.

If every member of a group could communicate directly with every other member of the group, only *one* interchange of information would end the game. However, such a communication system would require $n(n-1)$ channels. On the other hand, a minimal-cyclic structure has a solution time of $T = n - 1$, but it has only n channels. For some purposes we may be interested in the efficiency of a communication system as reflected by its economical use of channels. The number C of channels in a given structure is simply the sum of the elements of the structure matrix minus the number of elements in the major diagonal; thus we have

$$C = \sum_{i=1}^{n} \sum_{j=1}^{n} s_{ij} - n\,. \tag{8}$$

Now let us return to the structure matrix (2) of the three member group example. The status matrices associated with this structure are as follows:

$$\boldsymbol{I}_0 = \begin{pmatrix} 1 & 0 & 0 \\ 0 & 1 & 0 \\ 0 & 0 & 1 \end{pmatrix}, \quad \boldsymbol{I}_1 = \begin{pmatrix} 1 & 0 & 1 \\ 1 & 1 & 0 \\ 0 & 1 & 1 \end{pmatrix}, \quad \boldsymbol{I}_2 = \begin{pmatrix} 1 & 1 & 2 \\ 2 & 1 & 1 \\ 1 & 2 & 1\,. \end{pmatrix} \tag{9}$$

The solution time of this structure is 2 units, since $\boldsymbol{I}_2$ is the first status matrix containing no zeros. Notice, however, that three of the elements of $\boldsymbol{I}_2$ are 2's. This means that each member of the group received one primary element of information on two different occasions.

For some purposes such a repetition of information may be considered an advantage insofar as information received many times may perhaps be more likely accurate.

We may, however, be more interested in an economy of messages. This may be particularly true when the system is such that each message is very likely to be accurate. In this case it would be ideal if the solution matrix contained only 1's.

From the above considerations it would seem that the ratio $\mathcal{M}$ of the number of elements in the solution matrix (n^2) to the sum of the elements of that matrix could serve as a useful measure of the system's efficiency in regard to message economy; thus

$$\mathcal{M} = \frac{n^2}{\sum_{i,j=1}^{n} e_{ij}}. \tag{10}$$

It should be noted, however, that the sum of the elements of the solution matrix does not give the total number of messages sent. This sum is usually larger than the number of actual messages. To interpret the meaning of the operations between the structure and status matrices accurately, we must say that a given member who has received a primary element of information k times by the time t will *repeat* that element of information k times in all of the messages he sends at the time $t + 1$. Actually, this simply implies that the sum of the elements of the solution matrix reflects a "weighting" of the evils of redundance. It is as though this sum were saying: "It is bad to send the same information three times, but it is more than twice as bad to send it six times."

So far we have three possible measures of efficiency: the inverse of the solution time T^{-1}, the number of channels per member C/n, and the redundancy ratio $\mathcal{M}$.

Minimal-Cyclic Structure. In a minimal-cyclic structure the most remote member from any given member is $n-1$ steps away. This means that the solution time T of a minimal-cyclic structure is $n-1$ units. The efficiency of such a system (in regard to speed) drops linearly with increasing size of the group.

This structure has exactly 1 channel per member so that in this sense it is perfectly efficient.

By elementary considerations we find that the redundancy ratio $\mathcal{M}$ of a minimal-cyclic structure is given by the expression

$$\mathcal{M} = n/2^{n-1}. \tag{11}$$

This means that the redundancy rises sharply with increasing size of the group.

Theorem. The redundancy ratio $\mathcal{M}$ *of any series structure* $S_1S_2S_3 \cdots$ *which consists entirely of minimal-cyclic matrices is always less than* 1.

Proof: In order for the redundancy ratio $\mathcal{M}$ to be 1 it is necessary that all of the elements of the solution matrix also be 1. The determinant of such a matrix, however, is zero. This means that the ideal solution matrix is *singular.*

It can be readily shown that a minimal-cyclic matrix is never singular. But the solution matrix is given by a product of the form $S_1S_2 \cdots S_T$ in which all of the factors are non-singular matrices. The theorem follows from the fact that the product of a non-singular matrix with a non-singular matrix is also non-singular.

Partial Solution. An interesting variation of this game would be to stop it after a designated playing time. We would undoubtedly find that some structures had progressed further toward solution than others (as measured by the number of zeros in the final status matrix).

It may be that under certain circumstances a communication system of this kind is in constant danger of being completely blocked. It may also be that certain structures which are highly efficient according to the previously mentioned standards actually transmit most of the information just near solution time.

Such a structure would not be very useful in such "dangerous" circumstances, since its disruption before solution time would leave most of the members ignorant of most of the information.

Other structures not quite as efficient according to the previous standards may exhibit a rapidly growing spread of information in the system. If it were disrupted before solution time at least much of the information would have already been transmitted.

Also in this connection, if we permit negative numbers in the status matrices to represent false information and in the structure matrices to represent "chronic" liars, we would have situations analogous to the spreading and checking of false "rumors." Perhaps simple matrix operations can be devised to represent these phenomena.

Higher Order Information. So far the players of the game were all interested in only one question, namely, "What is the structure of the system"? In a *higher order* game the participants might be interested not only in what they know about the structure of the system, but also in *what everyone else knows* about the system.

The distribution of information in such a system can be represented by a matrix whose elements are also matrices. A discussion of such higher order games will appear in a subsequent paper.

This investigation is part of the work done under Contract No. AF 19(122)-161 between the U. S. Air Force Cambridge Research Laboratories and The University of Chicago.

LITERATURE

Landahl, H. D. and Richard Runge. 1946. "Outline of a Matrix Algebra for Neural Nets." *Bull. Math. Biophysics,* **8,** 75–81.

Landahl, H. D. 1947. "Outline of a Matrix Calculus for Neural Nets." *Bull. Math. Biophysics,* **9,** 99–108.

Landau, H. G. 1951. "On Dominance Relations and the Structure of Animal Societies. I. The Effect of Inherent Characteristics." *Bull. Math. Biophysics,* **13,** 1–19.

Luce, R. D. and A. D. Perry. 1949. "A Method of Matrix Analysis of Group Structure." *Psychometrika,* **14,** 95–116.

Luce, R. D. 1950. "Connectivity and Generalized Cliques in Sociometric Group Structure." *Psychometrika,* **15,** 169–90.

Polya, G. 1936. "Sur le nombre des isomères de certains composés chimiques." *Comptes Rendus Acad. Sci. Paris,* **202,** 1554–6.

Rapoport, A. 1949. "Outline of a Probabilistic Approach to Animal Sociology: I." *Bull. Math. Biophysics,* **11,** 183–96.

———. 1949. "Outline of a Probabilistic Approach to Animal Sociology: II." *Ibid.,* **11,** 273–81.

BULLETIN OF
MATHEMATICAL BIOPHYSICS
VOLUME 13, 1951

"ADDITION" AND "MULTIPLICATION" THEOREMS FOR THE INPUTS OF TWO NEURONS CONVERGING ON A THIRD

ANATOL RAPOPORT
COMMITTEE ON MATHEMATICAL BIOLOGY
THE UNIVERSITY OF CHICAGO

The output of a neuron innervated by two other neurons which, in turn, are subjected to two independent Poisson showers of stimuli, is derived as a function of the frequencies of the Poisson showers under two distinct assumptions, 1) where either of the two neurons can fire the third, and 2) where the stimuli from both neurons must impinge within a certain time interval to fire the third. For very small frequencies, the output of the third neuron is very nearly the sum of the input frequencies in the first case and proportional to the product of the input frequencies in the second case. Hence the designation "addition" and "multiplication" theorems. This treatment is a generalization of a previous treatment where the Poisson shower was assumed identical for the two outer neurons.

References to I, II, III, and IV will apply to a series of papers entitled "Contributions to the Probabilistic Theory of Neural Nets" (Rapoport, 1950a, 1950b, 1950c, 1950d). In III and IV we considered the output of a neuron N_3 subjected to stimuli from two other neurons, N_1 and N_2, which, in turn, were subjected to a single Poisson shower of stimuli. We now wish to generalize the problem by supposing that N_1 and N_2 receive separate independent Poisson showers of frequencies x and y respectively.

CASE 1. "ADDITION" OF FREQUENCIES. We shall first assume that a stimulus from either N_1 or N_2 can fire N_3 provided it does not fall within the refractory period of N_3, which, as in earlier papers, we designate by δ.

If the refractory period of all three neurons were zero, the output of N_3 would be simply $x + y$, the sum of the outside inputs. If the refractory period of N_3 only would be zero and that of N_1 and N_2 were δ, then the outputs of N_1 and N_2 would be $x/(\delta\, x + 1)$ and $y/(\delta\, y + 1)$ respectively (cf. I), but the output of N_3 would still be the sum of the outputs of N_1 and N_2. If, however, all three neurons have refractory period δ, the situation is more complicated. This is because the outputs of N_1 and N_2 are not Poisson-distributed and hence cannot be treated in the same way as the original "outside" input.

The Frequency Distribution of the Time of the First Firing. As in a previous paper (III), we wish to determine the probability frequency distribution of the time of the first firing of N_3, where the origin of time is chosen δ units following a firing. This distribution will in this more general case be different depending on whether that last firing was due to a stimulus from N_1 or from N_2. Let us suppose it was due to N_1. Then the probability frequency will be given by the following equation, which is a generalization of equation (6) of IV:

$$p_1(\delta, t) = xe^{-xt}\left[1 - \int_0^t \frac{y\,d\tau}{\delta y + 1}\right] + \frac{y}{\delta y + 1}\left[1 - \int_0^t xe^{-x\tau}\,d\tau\right] \tag{1}$$

$$= \frac{e^{-xt}}{\delta y + 1}\,[x + y + xy(\delta - t)], \quad \text{for } t \leqq \delta;$$

$$p_1(\delta, t) = xe^{-xt}\left[1 - \int_0^\delta \frac{y\,d\tau}{\delta y + 1} - \int_\delta^t \frac{y \exp(y\delta - y\tau)\,d\tau}{\delta y + 1}\right]$$

$$+ \frac{y \exp(y\delta - yt)}{\delta y + 1}\left[1 - \int_0^t xe^{-x\tau}\,d\tau\right] \tag{2}$$

$$= \frac{(x + y)\exp(y\delta - yt - xt)}{\delta y + 1}, \quad \text{for } t > \delta.$$

It can be readily verified that for $x = y$, equations (1) and (2) reduce to equations (8) and (9) of IV, as, of course, should be the case.

If we choose an initial firing due to N_2, then our frequency distribution will evidently be of the same form as (1) and (2) but with x and y interchanged, namely,

$$p_2(\delta, t) = \frac{e^{-yt}}{\delta x + 1}\,[x + y + xy(\delta - t)], \quad \text{for } t \leqq \delta; \tag{3}$$

$$p_2(\delta, t) = \frac{(x + y)\exp(x\delta - xt - yt)}{\delta x + 1}, \quad \text{for } t > \delta. \tag{4}$$

From these frequency distributions, the expected time of the first firing can be computed. For the distribution p_1, it is

$$\int_0^\infty t p_1(\delta, t)\,dt = \int_0^\delta \frac{te^{-xt}}{\delta y + 1}[x + y + xy(\delta - t)]\,dt$$
$$+ \int_\delta^\infty \frac{t(x+y)\exp(y\delta - yt - xt)}{\delta y + 1}\,dt \tag{5}$$
$$= \frac{x^2(1+\delta y) - y^2(1 - e^{-x\delta} - \delta x)}{x^2(x+y)(\delta y + 1)}.$$

For $p_2(\delta, t)$ we need only interchange x and y in (5) and obtain

$$\int_0^\infty t p_2(\delta, t)\,dt = \frac{y^2(1+\delta x) - x^2(1 - e^{-y\delta} - \delta y)}{y^2(x+y)(\delta x + 1)}. \tag{6}$$

As a check on the computations we note that both (5) and (6) reduce to (12) of IV for $x = y$, as should be the case.

Relative Frequencies of Firing due to N$_1$ *and* N$_2$. Equations (5) and (6) give the expected times of the next firing of N_3 following firings due to N_1 and N_2 respectively. To get the average expected time of the next firing, we must know how to weight the two known expected intervals, i.e., we must know the relative frequencies with which a firing of N_3 is due to N_1 and to N_2 respectively.

Selecting a firing of N_3 at random, let q_1 be the probability that it is due to a stimulus from N_1 and q_2 that it is due to a stimulus from N_2 $(q_1 + q_2 = 1)$. Moreover, let q_{12} be the probability that a firing due to N_2 follows one due to N_1, and analogously define q_{12}, q_{11}, and q_{22}. Then we have

$$\begin{aligned} q_1 &= q_1 q_{11} + q_2 q_{21} \\ q_2 &= q_1 q_{12} + q_2 q_{22}. \end{aligned} \tag{7}$$

Equations (7) state that a firing is due to N_1 if 1) either the preceding firing was due to N_1 and a firing due to N_1 followed it, or 2) the preceding firing was due to N_2 and a firing due to N_1 followed it; similarly for a firing due to N_2. The multiplications of the q's are justified, since the q's are actually conditional probabilities, e.g., "*given* that a firing is due to N_1, q_{12} is the probability that the next firing is due to N_2."

We now proceed to compute the q_{ij} $(i = 1, 2; j = 1, 2)$. We note that the first terms on the right sides of (1) and (2) give the probability frequency distribution of the time of the following occurrence: "The first stimulus following an instant δ units after a firing due to N_1 comes from N_1." Therefore, if we integrate the sum of these terms from zero to infinity, we shall obtain the probability that it occurs *at all,* i.e., the probability that the first impulse after δ units after a firing due to N_1 comes again from N_1. But this is q_{11}. Therefore

$$q_{11} = \int_0^\delta \left[x e^{-xt} \left(1 - \int_0^t \frac{y\,d\tau}{\delta y + 1} \right) \right] dt$$
$$+ \int_\delta^\infty \left[x e^{-xt} \left(1 - \int_0^\delta \frac{y\,d\tau}{\delta y + 1} - \int_\delta^t \frac{y \exp(y\delta - y\tau)}{\delta y + 1}\,d\tau \right) \right] dt. \tag{8}$$

Similarly,

$$q_{12} = \int_0^\delta \left[\frac{y}{\delta y + 1} \left(1 - \int_0^t x e^{-x\tau}\,d\tau \right) \right] dt$$
$$+ \int_\delta^\infty \left[\frac{y \exp(y\delta - yt)}{\delta y + 1} \left(1 - \int_0^t x e^{-x\tau}\,d\tau \right) \right] dt. \tag{9}$$

The expressions for q_{21} and q_{22} are obtained in an analogous manner. Performing the indicated operations we obtain

$$q_{11} = \frac{x^2(1 + \delta y) + y^2(e^{-x\delta} + \delta x - 1)}{x(x + y)(\delta y + 1)}, \tag{10}$$

$$q_{12} = 1 - q_{11}, \tag{11}$$

$$q_{22} = \frac{y^2(1 + \delta x) + x^2(e^{-y\delta} + \delta y - 1)}{y(x + y)(\delta x + 1)}, \tag{12}$$

$$q_{21} = 1 - q_{22}. \tag{13}$$

Equations (7) can be readily solved for q_1/q_2, namely,

$$q_1/q_2 = (1 - q_{22})/(1 - q_{11}). \tag{14}$$

Substituting the values of q_{11} and q_{22} from equations (10) and (13) into (14), we have

$$\frac{q_1}{q_2} = \frac{x[x^2(1 - e^{-y\delta}) + xy](\delta y + 1)}{y[y^2(1 - e^{-x\delta}) + xy](\delta x + 1)}. \tag{15}$$

Finally, since $q_1 + q_2 = 1$, we obtain

$$q_1 = \frac{x[x^2(1 - e^{-y\delta}) + xy](\delta y + 1)}{x[x^2(1 - e^{-y\delta}) + xy](\delta y + 1) + y[y^2(1 - e^{-x\delta}) + xy](\delta x + 1)}, \tag{16}$$

$$q_2 = \frac{y[y^2(1 - e^{-x\delta}) + xy](\delta x + 1)}{x[x^2(1 - e^{-y\delta}) + xy](\delta y + 1) + y[y^2(1 - e^{-x\delta}) + xy](\delta x + 1)}. \tag{17}$$

The average time between firings will then be obtained by the weighted sum (where the weighting factors are q_1 and q_2) of the right sides of (5) and (6) increased by δ, namely,

$$\bar{t} = \delta + q_1 \int_0^\infty t p_1(\delta, t)\,dt + q_2 \int_0^\infty t p_2(\delta, t)\,dt, \tag{18}$$

which, after elementary but laborious computation, gives

$$\begin{aligned} \bar{t} = \delta + \{ & y[x^2(1 - e^{-y\delta}) + xy][x^2(1 + \delta y) - y^2(1 - e^{-x\delta} - \delta x)] \\ & + x[y^2(1 - e^{-x\delta}) + xy][y^2(1 + \delta x) \\ & - x^2(1 - e^{-y\delta} - \delta y)]\}\,\Delta^{-1}, \end{aligned} \tag{19}$$

where

$$\begin{aligned} \Delta = xy(x + y)\{ & [x^3(1 - e^{-y\delta}) + x^2 y](\delta y + 1) \\ & + [y^3(1 - e^{-x\delta}) + xy^2](\delta x + 1)\}. \end{aligned} \tag{20}$$

The frequency of N_3 is then

$$\begin{aligned} 1/\bar{t} = \Delta\{ & \Delta\,\delta + y[x^2(1 - e^{-y\delta}) \\ & + xy][x^2(1 + \delta y) - y^2(1 - e^{-x\delta} - \delta x)] \\ & + x[y^2(1 - e^{-x\delta}) + xy][y^2(1 + \delta x) \\ & - x^2(1 - e^{-y\delta}) - \delta y]\}^{-1}. \end{aligned} \tag{21}$$

For $x = y$, equation (21) reduces to (14) of IV. For very small values of δ (or, which is the same thing, for very small values of x

and y), it is seen that $x + y$ is a first approximation. Taking somewhat larger values of δ (or of x and y), it can be verified that $x(\delta x + 1)^{-1} + y(\delta y + 1)^{-1}$ is a second approximation, which would be exact if a refractory period were assumed for N_1 and N_2 but neglected for N_3. For large values of δ (or for x and y) equation (21) reduces to δ^{-1}, the maximal frequency of N_3.

A. Shimbel (1949) used the following approximation for the output of $N_3 : f_3 = f_1 + f_2 - \delta f_1 f_2$, where f_1, f_2, and f_3 denote the respective outputs of N_1, N_2, and N_3. In our notation this would read

$$1/\bar{t} = x(\delta x + 1)^{-1} + y(\delta y + 1)^{-1} - \delta xy[(\delta x + 1)(\delta y + 1)]^{-1}.$$

This approximation agrees closely with formula (21) for both very small and very large values of x and y.

CASE 2. MULTIPLICATION OF FREQUENCIES. We may consider the "multiplication" of the inputs of N_1 and N_2 in its simplest form by neglecting the refractory period. If successive stimuli from a *single* neuron can sum to fire N_3, the case reduces to that of a single neuron subject to a Poisson shower of stimuli. This case was treated in II. We shall suppose next that two stimuli *one from each shower* are required to fire N_3. Then, if x and y are the respective frequencies of the showers, a stimulus from a given shower is effective if, and only if, it is preceded within σ units (where σ is the period of latent addition) by a stimulus received from the other shower. Thus the probability that a stimulus from N_1 is effective will be $1 - e^{-y\sigma}$, and the probability that a stimulus from N_2 is effective will be $1 - e^{-x\sigma}$. The frequency of effective stimuli will then be

$$x(1 - e^{-y\sigma}) + y(1 - e^{-x\sigma}), \tag{22}$$

which for small values of x and y reduces to $2xy\sigma$.

If, on the other hand, x and y are large, the frequency approaches $x+y$ and increases with x and y without bound. We wish to compute the frequency of N_3 where δ is the refractory period of all three neurons and thus provides an upper bound (δ^{-1}) to their frequencies.

For simplicity of treatment it will first be assumed that $x = y$. The generalization to the case of independent inputs x and y will then become apparent, and, moreover, the special case of equal inputs will provide a running check on the laborious computations. We shall also assume that $\sigma < \delta/2$. This condition insures that no three consecutive stimuli impinging upon N_3 may fall within an interval of σ units.

We define as a "potentially effective" pair of stimuli a pair which fall within σ units of each other. The condition $\sigma < \delta/2$ implies not only that the stimuli of such a pair come from different neurons, but also that the potentially effective pairs are "isolated" from each other, i.e., a stimulus can belong to at most one such pair.

Consider first the frequency of potentially effective pairs. It was shown in III that if an arbitrary instant is chosen on the time axis of, say, N_1 without knowledge of the time of its last firing, then the probability frequency distribution of its next (or last) firing is constant for an interval of length δ. That is, if the arbitrarily chosen instant is taken as the origin, the frequency distribution for the interval $(0, \delta)$ will be given by $x(\delta x + 1)^{-1}$. Therefore if a stimulus from N_1 is chosen, the probability that it is preceded by another stimulus within σ units (which necessarily must come from N_2 since $\sigma < \delta$) is $x\sigma(\delta x + 1)^{-1}$. Since the frequencies of N_1 and N_2 are both $x(\delta x + 1)^{-1}$ (cf. I), the total frequency of stimuli *received* by N_3 is evidently $2x(\delta x + 1)^{-1}$. Therefore the frequency of those stimuli which are preceded within σ by other stimuli (the frequency of potentially effective pairs) is $2x^2\sigma(\delta x + 1)^{-2}$. Not all of these pairs, however, can be effective in firing N_3, since one or the other of a potentially effective pair may fall within the refractory period of N_3. Our task is now to compute the fraction of such potentially effective stimuli which are not actually effective.

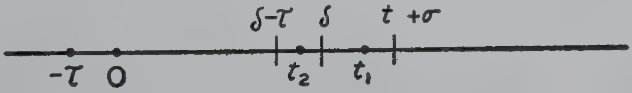

FIGURE 1

In Figure 1, 0 indicates the origin of time and also a firing instant of N_3. The neuron N_3 has fired at $t = 0$, because N_1 and N_2 have fired within the interval $\tau < \sigma$, neither of the stimuli falling within the refractory period δ of N_3.

Consider now the conditions under which the next pair of stimuli falling within σ units (a potentially effective pair) will be actually *ineffective.* This can happen only if one or both of the stimuli from N_1 and N_2 fall within the refractory period of N_3 which lasts until δ (see Fig. 1). But the stimulus from N_1 cannot fall within this interval since N_1 is itself refractory for δ units following its firing at 0. Thus a necessary condition for the ineffectiveness of the next potentially effective pair is that the stimulus from N_2 fall somewhere at $t_2 < \delta$. Because N_2 is refractory from $-\tau$ to $\delta - \tau$, t_2 falls in the interval $(\delta - \tau, \delta)$.

Now the necessary and sufficient condition that the next potentially effective pair be ineffective is that in addition to the stimulus from N_2 falling at t_2, the stimulus from N_1 should fall at t_1, such that $t_1 - t_2 < \sigma$. Otherwise the stimulus at t_2 will not be a member of a potentially effective pair, N_3 will not fire in the interval $(0, t_2 + \sigma)$, and the next potentially effective pair will fall wholly outside of δ, i.e., it will be actually effective. Hence to compute the probability that the next potentially effective pair after $t = 0$ be ineffective is equivalent to computing the probability that the stimuli from N_1 and N_2 fall at t_1 and t_2 as shown in Figure 1.

This probability, in view of the theory developed in III, is given by

$$f = \frac{1}{\sigma} \int_0^\sigma d\tau \int_{\delta-\tau}^{\delta} x \exp(x\delta - x t_2 - x\tau)\, dt_2 \cdots \int_\delta^{t_2+\sigma} x \exp(x\delta - x t_1)\, dt_1. \tag{23}$$

The limits of the last integral indicate that t_1 must fall beyond δ, but it must fall within σ of t_2, if there is to be a potentially effective pair. The limits of the middle integral indicate that t_2 must fall beyond $\delta - \tau$, but it must fall before δ for the pair to be actually ineffective. The first integral indicates that τ can range with equal probability from 0 to σ for the effectiveness of the initial pair at $-\tau$ and 0. The computation of f is straightforward and yields

$$f = 1 - \frac{3 - 4e^{-x\sigma} + e^{-2x\sigma}}{2x\sigma}. \tag{24}$$

The quantity f represents the fraction of actually ineffective pairs *following* actually effective pairs. But the *only* ineffective pairs are those following effective pairs, as shown by the argument above. Hence f represents the fraction of ineffective pairs for every effective pair. Therefore the fraction of all the pairs which *are* effective must be

$$f' = (1 + f)^{-1} = \frac{2x\sigma}{4x\sigma - 3 + 4e^{-x\sigma} - e^{-2x\sigma}}, \tag{25}$$

and this is the correction factor which must modify the frequency of potentially effective pairs to give us the actual frequency of N_3.

The frequency of N_3 is thus seen to be

$$\frac{2x^2\sigma f'}{(\delta x+1)^2}=\frac{4x^3\sigma^2}{(\delta x+1)^2[4x\sigma-3+4e^{-x\sigma}-e^{-2x\sigma}]}. \qquad (26)$$

For very small x, we have the approximation $2x^2\sigma$, which indicates that one of every potentially effective pair of stimuli fires N_3. For very large x, equation (26) reduces to σ/δ^2, and, in particular, if σ takes its maximum permissible value, $\delta/2$, the frequency will be $1/2\delta$, which is intuitively evident.

To generalize (26) to the case in which the inputs impinging upon N_1 and N_2 have independent frequencies x and y, we must compute f_1 and f_2, the respective probabilities that a potentially effective pair following a firing due to N_1 or such a pair following a firing due to N_2 is ineffective. The probability f_1 is given by a generalization of equation (23), namely,

$$f_1=\frac{1}{\sigma}\int_0^\sigma d\tau\int_{\delta-\tau}^{\delta} y\exp(y\delta-yt_2-y\tau)\,dt_2$$
$$\cdots\int_\delta^{t_2+\sigma} x\exp(x\delta-xt_1)\,dt_1. \qquad (27)$$

This yields

$$f_1=\frac{x(x+y)(y\sigma+e^{-y\sigma}-1)-y^2(1-e^{-x\sigma})+xye^{-x\sigma}(1-e^{-y\sigma})}{xy\sigma(x+y)}. \qquad (28)$$

It can be easily seen that f_2 is obtained from f_1 by interchanging x and y, namely,

$$f_2=\frac{y(x+y)(x\sigma+e^{-x\sigma}-1)-x^2(1-e^{-y\sigma})+xye^{-y\sigma}(1-e^{-x\sigma})}{xy\sigma(x+y)}. \qquad (29)$$

On the other hand, the frequency of potentially effective pairs is symmetric in x and y and is given by $2xy\sigma[(\delta x+1)(\delta y+1)]^{-2}$. Therefore for every two firings there are f_1+f_2 ineffective pairs, and the correction factor turns out to be

$$f=\frac{2}{f_1+f_2+2}. \qquad (30)$$

Combining these results, we obtain our "multiplication theorem," i.e., the output of N_3 subject to stimuli from N_1 and N_2 which must "sum" to produce a firing, namely,

$$\begin{aligned}2x^2 y^2 \sigma^2 (x + y) [(\delta x + 1) (\delta y + 1)]^{-1} \\ \times [x^2 (2y\sigma + e^{-y\sigma} - 1) + y^2 (2x\sigma + e^{-x\sigma} - 1) \\ + xy (e^{-x\sigma} + e^{-y\sigma} - e^{-(x+y)\sigma} - 1)]^{-1}.\end{aligned} \tag{31}$$

For $x = y$, (31) reduces to (26). For small and for large values of x and y, approximations analogous to those in the previous case are obtained.

This work was aided by a grant from the Dr. Wallace C. and Clara A. Abbott Memorial Fund of The University of Chicago.

LITERATURE

Rapoport, A. 1950a. “Contribution to the Probabilistic Theory of Neural Nets: I. Randomization of Refractory Periods and of Stimulus Intervals.” *Bull. Math. Biophysics*, **12**, 109–21.

———. 1950b. “Contribution to the Probabilistic Theory of Neural Nets: II. Facilitation and Threshold Phenomena.” *Ibid.*, **12**, 187–97.

———. 1950c. “Contribution to the Probabilistic Theory of Neural Nets: III. Specific Inhibition.” *Ibid.*, **12**, 317–25.

———. 1950d. “Contribution to the Probabilistic Theory of Neural Nets: IV. Various Models for Inhibition.” *Ibid.*, **12**, 327–37.

Shimbel, A. 1949. “Input-Output Problems in Simple Nerve-Ganglion Systems.” *Bull. Math. Biophysics*, **11**, 165–71.

BULLETIN OF
MATHEMATICAL BIOPHYSICS
VOLUME 13, 1951

CONTRIBUTIONS TO THE MATHEMATICAL BIOLOGY OF EXCITATION WITH PARTICULAR EMPHASIS ON CHANGES IN MEMBRANE PERMEABILITY AND ON THRESHOLD PHENOMENA

George Karreman
Committee on Mathematical Biology
The University of Chicago

Simple chemical reactions of Ca^{++} and K^+ ions with a P^- ion in a membrane are assumed to be causes of changes in permeability of that membrane to K^+ ions. On the basis of such a mechanism a quantative concept of membrane permeability to K^+ ions is defined. The diffusion of K^+ ions through such a membrane is studied mathematically in a simplified version. An applied electrical field as well as the diffusion potential of the K^+ ions are considered to effect the chemical equilibrium constants of the proposed reactions. It is shown that such a system, which can be described by a set of nonlinear differential equations, may have two stable states of equilibrium which are separated by an unstable equilibrium state. As a consequence, such a system may possess a threshold. Estimations of resting potential, threshold—electrical as well as chemical—and of permeability increase, together with that of the corresponding electrical field strength are shown to have the correct order of magnitude. A possible way to derive the one-factor theory from a physical mechanism as considered here is outlined. It is pointed out that the dependence of the thresholds and the permeability changes on several parameters might be calculated on the basis of such a mechanism. As an example it is shown how in principle some of these relations are derived. Furthermore, the time course of excitatory disturbance for different intensities of the initial disturbance are derived theoretically for the case of chemical stimulation. The curves so obtained show a striking similarity in all the characteristic features with the corresponding ones which are obtained experimentally for the case of electrical stimulation of nerve. These results suggest that response to electrical and chemical stimulation is based on a common threshold phenomenon such as considered here. Finally, a more detailed mathematical description, which takes into account explicitly the diffusion of K^+ ions through the membrane for a finite thickness of the membrane is outlined. The equations obtained, which seem to be infeasible of solution at the present time, suggest that it is plausible that relaxation oscillations with a threshold can be derived on the basis of such a mechanism as proposed here. Qualitative agreement with experimental evidence is indicated.

The concept of threshold is a typical bio-mathematical concept and plays a basic role in electrophysiology (see, e.g., Schaefer, 1940) and the mathematical biology of the (central) nervous system (Rashevsky, 1948). Some suggestions as to the quantum-physical nature of this concept were made by A. Bethe (1937) and P. Jordan (1944).

An attempt to derive the all-or-none law on a probabilistic basis was made by H. von Schelling (1944). A formal attempt in connection with subthreshold potentials based on an electrical model of a membrane-element, the resistance of which is assumed to be a nonlinear function of the potential difference across the membrane, was made by B. Katz (1947). Another mechanism which exhibits threshold effects was derived by A. Rapoport (1950) from a probabilistic treatment of neural nets.

I. Tasaki and T. Takeuchi (1941) obtained an action curve from one node. As an estimate of the length of one node we might take (cf., e.g., Engström and Lütky, 1950) as high a value as 3×10^{-3} cm, while the liminal length is of the order of 10^{-1} cm (Rushton, 1937). From these estimates we may infer that propagation along one node is not very likely. The result mentioned above of Tasaki and Takeuchi would then be an example of local excitation without propagation, which still gives an action curve. Furthermore, according to Tasaki (1940), the all-or-none law holds, in general, for excitation of a single node.

One of the postulates of the formal theory of W.A.H. Rushton (1937) underlying much recent experimental work (e.g., Katz, 1937; 1939) corresponds to a local threshold. It is, in fact, assumed in this theory that the local condition of the membrane suddenly changes after the resting charge of the membrane has been altered by a critical amount θ_1. From equation (8) of Rushton's paper (*loc. cit.*), it follows that the liminal length is greater than zero only if the critical value θ_1 is greater than zero. The latter would correspond to a local threshold.

In the formal theory of Katz (*loc. cit.*) a threshold mechanism is discussed for one membrane-element only. This would, therefore, also correspond to a local threshold.

A. M. Weinberg (1942) has pointed out that the only thing which can be concluded from the experimental curves describing the subliminal responses of nerve (Katz, 1937, and others mentioned in Weinberg's paper) is that the subsidence of the excitatory state ε is not described by the usual linear differential equations of the one- or two-factor theories, but should be described by a nonlinear differential equation, in which the time-constant is itself a function of ε. Furthermore, he has pointed out that an interpretation of the deviations from linearity in terms of a "local response" in accordance with Rushton's notion of liminal length (*loc. cit.*; Katz, 1939) is somewhat irrelevant from the strictly phenomenological viewpoint, a physical interpretation of such a nonlinearity being outside the scope of a formal theory. A local threshold is postulated also in the two-factor theory of nerve conduction (Rashevsky, 1948).

In the light of what has been mentioned above, one might believe that it is plausible that a local threshold exists. It is also conceivable that a threshold for the longitudinal gradient of the "polarization" exists (cf. Eichler, 1933; also Katz, 1937, 1939). And it may very well be that those thresholds, if they both exist, are not independent of each other; it is conceivable that the latter threshold might be derived from the former one. We realize that the phenomenon of excitation and propagation is probably described by one, or several, (very difficult) partial differential equations or integrodifferential equations. It would then seem to be artificial to concentrate too much on either the "local" or the "longitudinal" aspect of the problem. However, these exact equations are still unknown at the present time. Therefore we will focus attention here on the local aspect of the process. After what has been said above in relation to work of Tasaki and Takeuchi, Tasaki, Rushton, Katz, and Weinberg, we feel justified in doing this. We would like to remark here, however, that it is conceivable that even if the local response process is essentially a threshold phenomenon, it may appear to be graded (for a different suggestion, see Katz, 1937). This may be due to a combination of several factors. Namely, the stimulation may be "parametric," by which we mean that as a result of the stimulation the conditions are changed with, as a consequence, a change in threshold of the response process. These changes and their consequences may very well be graded. Or, due to experimental techniques, the threshold of local stimulation may be masked either by stimulating too large an area (e.g., by electrical spread or leakage) or by large gradients at the borders of the stimulated area. In this relation the method used by Tasaki, Tasaki and Takeuchi in the papers mentioned above might be preferable. As a matter of fact, as stated above, they obtained an action current in this way from an excited region much shorter than the liminal length, while Tasaki concluded that the all-or-none law holds for such a process.

The importance of relaxation oscillations in relation to the response of tissues to stimuli has been realized for some time. B. van der Pol and J. M. van der Mark (1928) have compared the rhythmic heartbeat with a relaxation oscillation and have pointed out several similarities between the two (e.g., heart block and demultiplication of frequency). A. Fessard (1931) also emphasized the similarity between relaxation oscillations and neural rhythms. Later work of Fessard (1936) and A. Arvanitaki (1938a, b; 1939) also points in the direction of the occurrence of relaxation oscillations in the case of stimulated nerves and myocardium. At this point it might also be of some interest to mention the model experiments of Bethe (1943), O. Schäfer (1943), Bethe and H. Schaefer (1947). D. Auger (1936) found many similarities in this respect between the response of animal and plant cells to stimulation. N. Rashevsky's suggestion for deriving a threshold for relaxation oscillations was elaborated by the author (Karreman, 1949), who was unaware that the theory of these so-called "hard oscillation" cases had already been developed to a certain extent previously (Andronow and Chaikin, 1937; 1949). The problem has been treated recently also by N. Minorsky (1947). These "hard oscillation" cases, with threshold properties, occur, mathematically speaking, if there are at least two limit cycles around a stable singular point, the first one being unstable, the second one stable (Fig. 1).

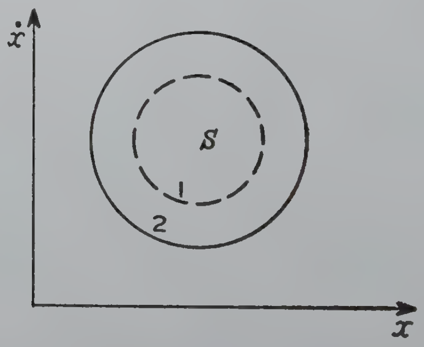

FIGURE 1. Phase plane representing a "hard oscillation." S is a stable singular point, 1 and 2 are limit cycles which are unstable and stable respectively.

The theory of self-excited oscillations has been, to a large extent, based on ideas and work of H. Poincaré (1892). Analytical treatments have also been given by, e.g., van der Pol (1926) and N. Kryloff and N. Bogoliuboff (1937; 1949). It has had many important applications in the case of oscillations of mechanical and electrical systems. In the case of excited muscle and nerve fibers transition through an unstable state or region has been observed (Rushton, 1932; cf. also R. S. Lillie, 1923). Some theoretical approaches in this direction have been made by K. F. Bonhoeffer et al. (1948a through f), together with experimental investigations of the activation of a passive iron wire as a model for the excitation of nerve. R.

S. Lillie had made similar investigations previously (1923, 1924) to get a model for the transmission of nerve impulses. Weinberg (1942) has pointed out the analogy with nonlinear electrical and mechanical systems by constructing a "local phenomenological characteristic" from experimental data (Katz, 1937) on subliminal responses of nerve. In Weinberg's paper several other investigators are quoted who have suggested that the excitation equations are nonlinear.

According to the Membrane Theory proposed by J. Bernstein (1902) the resting potential across the membrane of a nerve or muscle fiber is ascribed to the selective permeability to potassium ions which are present inside the fiber in a concentration which is higher than the normal concentration outside it. K. S. Cole and H. J. Curtis (1938) showed that during activity of Nitella the transverse resistance drops temporarily, suggesting a structural breakdown of the membrane and, as a result, a temporary loss of selective permeability to ions. They (*loc. cit.*; 1939) have also been able to show a close relation between the change of the membrane electromotive force and that of the conductance of the membrane. They consider the sudden changes in those quantities to be connected with the activity which is responsible for the all-or-none law and the initiation and propagation of the nerve impulse. Their results for the squid giant axon correspond to those previously found for Nitella (Cole and Curtis, 1938). There are also suggestions (cf. Schaefer, 1940) that potassium ions effect the structure of the membrane. Furthermore, A. L. Hodgkin (1947) has found that the conductance of the membrane is increased about three-fold when the external potassium concentration is trebled. In addition, there is some evidence that diffusion of potassium ions does play a role in the process of the development of the action potential of giant nerve fibers (Webb and Young, 1940) and that of the giant plant cell Nitella (Osterhout, 1934; Hill and Osterhout, 1934). The latter investigators consider, as a good approximation in the case of Nitella, the diffusion of potassium ions only.* Assuming with Cole and Curtis (1940) that the membrane conductance is a measure of its permeability to ions we see that potassium ions cause an increase of that permeability, presumably (Schaefer, 1940) by causing a so-called "loosening-up" of the membrane; while calcium ions, in general, decrease the ion permeability of the membrane (cf. R. S. Lillie, 1923; Schaefer, 1940). The increase in permeability at the cathode and the decrease in permeability at the anode might be due (cf. Schaefer, 1940) to this effect of K and Ca if we keep in mind that the concentration of K in the inside of the fiber is greater (and relatively more than that of Ca) than in the outside (Webb and Young, *loc. cit*; von Muralt, 1945) and both ions travel to the cathode from the anode. The importance of structural changes of surface membranes in relation to stimulation had already been stressed by R. S. Lillie (1923). It has been suggested (Heilbrunn, 1943) that during stimulation Ca ions are released from a compound in the cell surface by, e.g., potassium ions. Heilbrunn considers as essential for stimulation a colloid chemical reaction produced by calcium, similar to blood clotting. He and his coworkers have given evidence to that effect in the case of stimulation of lower organisms (for example, Amoeba proteus). In our opinion this scheme is not very likely to account for fast reactions such as occur, e.g., during the stimulation of nerve fibers, since the duration of the action potential is only of the order of milliseconds. We will, therefore, consider a membrane with only one or more layers composed of a calcium compound and will investigate here the diffusion of potassium ions through such a membrane, assuming that the latter are able to react with the calcium compound. According to R. Höber (1945) excitation is a reversible increase of permeability to ions. True enough, Höber considers, with many others, the latter brought about by a transitory dispersion of the colloidal structure of the plasma membrane. These colloidal changes are still hard to treat theoretically, though recent advances in this field (cf. Verwey and Overbeek, 1948) might be very helpful.

---

*Very recent investigations (Hodgkin, Huxley, and Katz, 1949), which, unfortunately, came to our attention after the major part of this work had been done, indicate that the increase in the permeability to sodium precedes that of the permeability to potassium in the case of the squid giant nerve fiber during action.

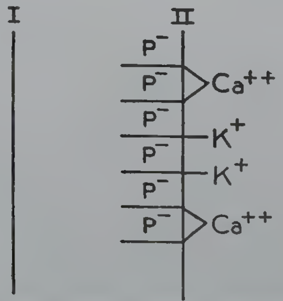

FIGURE 2. Model of a membrane which changes its permeability in accordance with the chemical reaction (1). The numerals I and II represent the inner and outer boundaries of the membrane.

Model of a membrane. We will assume that a compound of Ca ,

CaP_2, in which P may represent a fatty acid ion or a lipoid constituent, forms a layer in the membrane. The latter may be mono- or bimolecular (Höber, 1945; Danielli and Davson, 1935) as shown in Figure 2. Potassium ions are supposed to react with this compound (Heilbrunn, 1943) in the following way:

$$CaP_2 + 2K^+ \rightleftarrows Ca^{++} + 2KP. \qquad (1)$$

The KP formed by this reaction might be said to produce a "hole" (cf. Höber, 1945; Fleckenstein, 1942), as shown in Figure 2. This concept of hole is, of course, much too simple and much too crude. Instead, the interactions of the Ca^{++}, P^- and K^+ ions should be taken into account in much more detail. Yet it is interesting to see what consequences, particularly quantitative ones, can be drawn from it.

Instead of using the highly oversimplified reaction (1) we will investigate the more appropriate scheme:

$$CaP_2 \rightleftarrows CaP^+ + P^-, \qquad (2)$$

$$CaP^+ \rightleftarrows Ca^{++} + P^-, \qquad (3)$$

$$P^- + K^+ \rightleftarrows KP, \qquad (4)$$

which corresponds to Figure 3.

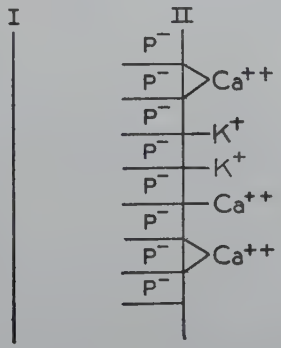

FIGURE 3. Improved model of a membrane which changes its permeability in accordance with the chemical reactions (2), (3), and (4).

We will call the equilibrium constants of these reactions K_1, K_2, and K_3^{-1} respectively. We assume here that we may apply the laws of chemical equilibrium and use the concept of concentration even though we may be dealing with pauci-molecular layers in the membrane. Then we have:

$$K_1 = \frac{(\mathrm{CaP_2})}{(\mathrm{CaP^+})\,(\mathrm{P^-})}, \tag{5}$$

$$K_2 = \frac{(\mathrm{CaP^+})}{(\mathrm{Ca^{++}})\,(\mathrm{P^-})}, \tag{6}$$

$$K_3^{-1} = \frac{(\mathrm{K^+})\,(\mathrm{P^-})}{(\mathrm{KP})}, \tag{7}$$

where parenthesis denote molar concentrations.

Denoting by P_0 the total concentration of $\mathrm{P^-}$ we find:

$$2(\mathrm{CaP_2}) + (\mathrm{CaP^+}) + (\mathrm{KP}) + (\mathrm{P^-}) = P_0\,. \tag{8}$$

We regard the P_0 as determined by metabolic reactions.

Elimination of $(\mathrm{CaP_2})$, $(\mathrm{CaP^+})$ and (KP) from (5), (6), (7) and (8) gives:

$$\begin{aligned} 2K_1K_2(\mathrm{Ca^{++}})\,(\mathrm{P^-})^2 + \{K_2(\mathrm{Ca^{++}}) \\ + K_3(\mathrm{K^+}) + 1\}(\mathrm{P^-}) - P_0 = 0\,. \end{aligned} \tag{9}$$

This equation determines $(\mathrm{P^-})$. The two roots of (9) have different signs as can be easily seen. Of course, only the positive root of this equation for $(\mathrm{P^-})$ has a physical meaning.

The first basic assumption we will make is as follows. The permeability h of the membrane to potassium ions is proportional to the number of "holes." The latter number we assume to be proportional to $(\mathrm{KP}) + (\mathrm{P^-})$. Of course, more appropriate (better weighted) combinations of (KP), $(\mathrm{P^-})$, and $(\mathrm{CaP^+})$ might have been chosen. However, a serious difficulty, due to lack of sufficient available data, is to decide at present which combination or function of these concentrations should be taken as a measure of the permeability of the membrane to potassium ions. The different fields of force between the ions should be taken into account, as well as the different masses and, therefore, different moments of inertia, the latter being important for the rotation of the molecules involved.

On the basis of these assumptions we find:

$$a\,h = (\mathrm{KP}) + (\mathrm{P^-}), \tag{10}$$

a being a constant of proportionality.

Through these assumptions, essentially described by equations (2), (3), (4), (8), and (10), the above-mentioned antagonistic influences of $\mathrm{Ca^{++}}$ and $\mathrm{K^+}$ ions on the permeability of membranes is introduced.

Elimination of (KP) from (7) and (10) gives:

$$a\,h = K_3(\mathrm{K}^+)(\mathrm{P}^-) + (\mathrm{P}^-). \tag{11}$$

Solving (11) for (P^-) we find:

$$(\mathrm{P}^-) = \frac{a\,h}{K_3(\mathrm{K}^+) + 1}. \tag{12}$$

Introducing (12) into (9) and rearranging leads us to:

$$\frac{2K_1K_2(\mathrm{Ca}^{++})\,\alpha^2}{\{K_3(\mathrm{K}^+) + 1\}^2}h^2 + \frac{K_2(\mathrm{Ca}^{++}) + K_3(\mathrm{K}^+) + 1}{K_3(\mathrm{K}^+) + 1}\,\alpha\,h - P_0 = 0. \tag{13}$$

This quadratic equation in h determines h as a function of (K^+) and of (Ca^{++}).

We now introduce the following notations:

$$\begin{aligned} (\mathrm{K}^+) &= c\,, \\ 2K_1K_2(\mathrm{Ca}^{++})\,\alpha^2 &= a\,, \\ K_3 &= b\,, \\ K_2(\mathrm{Ca}^{++})\,\alpha &= d\,. \end{aligned} \tag{14}$$

We then can rewrite (13) for $h = h(c)$ as follows:

$$\frac{a}{(bc+1)^2}\left\{ h(c) \right\}^2 + \frac{d}{bc+1}h(c) + \alpha\,h(c) - P_0 = 0. \tag{15}$$

It is easy to see that the function $h(c)$ determined by (15) is

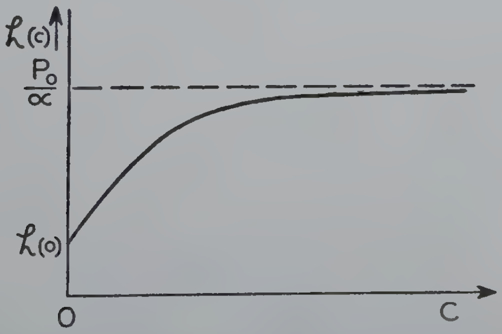

FIGURE 4. Illustration of the relation between the permeability to potassium ions and the concentration of those ions in the membrane on the basis of a mechanism defined by equations (2), (3), (4), (8), and (10).

such that $h(0) > 0$, while $h(c)$ approaches $\frac{P_0}{a}$ if c approaches infinity (which is, of course, beyond the physiological limits). Similarly, $h = \frac{P_0}{a}$ for $(\mathrm{Ca}^{++}) = 0$, implying $a = d = 0$. Furthermore, it can be shown [most easily by differentiation of both sides of (15) with respect to c and using the fact that physiologically $h(c) > 0$] that $h'(c) > 0$ and $h''(c) < 0$ for all positive c [and $h(c)$]. Therefore, plotting $h(c)$ against c we obtain a curve like the one shown in Figure 4.

For later use we will only mention here the dependence of the slope of the curve shown in Figure 4 on the concentration c. It is given by:

$$h'(c) = \frac{\{2ah(c) + df(c)\}\, bh(c)}{\{2ah(c) + df(c) + a f^2(c)\}\, f(c)}, \tag{16}$$

$f(c)$ being an abbreviation for

$$f(c) = 1 + bc\,.$$

The diffusion of potassium through the proposed membrane. We will now consider the diffusion of potassium through a membrane of the type outlined in Figure 3. We suppose, as is the case with several living membranes (Höber, 1945), that at one side of the membrane the potassium has the concentration K_1 and at the other side $K_2 \neq K_1$. As is mentioned above, the approximation which considers the diffusion of potassium alone through one or more membranes is the one actually considered by S. E. Hill and W. J. V. Osterhout in a

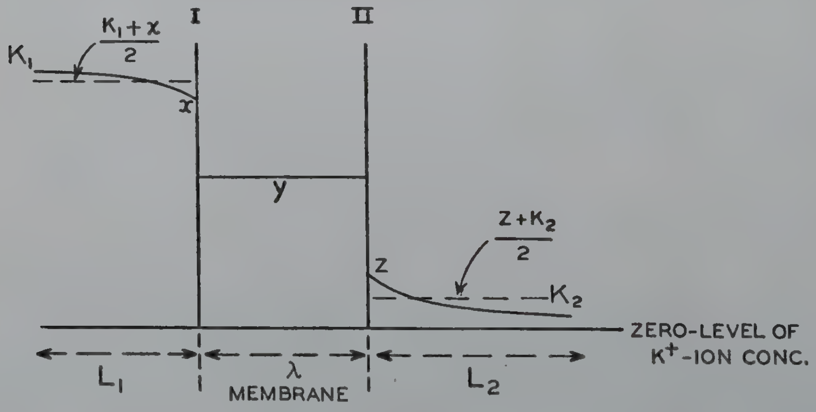

FIGURE 5

long series of papers on the action potentials of the giant plant cell Nitella (e.g., Osterhout, 1934; Hill and Osterhout, 1934; Osterhout and Hill, 1934; 1938). These action potentials have some features in common with those of nerve and muscle fibers.* They also share common features with those of the heart. According to Webb and Young (1940) the diffusion of potassium ions appears to be a principal factor responsible for the development of the action potential. In nerve and muscle fibers, as well as in Nitella cells, the inside concentration K_1 of potassium ions is much greater than their outside concentration K_2 (Höber, 1945). Therefore, we will consider the situation shown in Figure 5.

At both sides of the membrane there are two layers. The first layer, of thickness L_1, is the one in which the diffusion of potassium ions from the high potassium ion concentration K_1 to that (x) just inside the membrane occurs. The other layer, of thickness L_2, is the one in which the diffusion of potassium ions from the concentration (z) just outside the membrane to the low outside concentration K_2 takes place. We will consider the average concentrations in these layers

$$\frac{K_1 + x}{2} \quad \text{and} \quad \frac{z + K_2}{2}$$

respectively, use the approximation method developed by Rashevsky (1948) and take for the permeabilities† of the inside layer I the value $h(x)$; for that of the outside layer II the value $h(y)$. Assuming the chemical reactions to be very fast compared with the diffusion processes, so that they may be considered always to be in equilibrium, we may suppose $h(x)$ and $h(y)$ to be determined by the same type of mechanism as described by equations (2), (3), and (4). Therefore, $h(x)$ and $h(y)$ themselves are determined by an equation of the type (15) with $c = x$ and $c = y$, respectively. Using the approximation method we now find the equations describing the conservation of K^+ ions in both diffusion layers and in the membrane:

$$AL_1 \frac{d\dfrac{K_1 + x}{2}}{dt} = AD_1 \frac{K_1 - x}{L_1} - Ah(x)(x - y), \tag{17}$$

---

*Very recently important differences have been pointed out (Hodgkin, 1949).

†Where we speak of permeability in the future we mean the permeability to potassium ions.

$$A\,\lambda \frac{dy}{dt} = Ah(x)\,(x-y) - Ah(z)\,(y-z)\,, \tag{18}$$

$$AL_2 \frac{d\dfrac{z+k_2}{2}}{dt} = Ah(z)\,(y-z) - AD_2 \frac{z-K_2}{L_2}\,, \tag{19}$$

A being the cross-section.

Equations (17), (18), and (19) form a set of three simultaneous, nonlinear differential equations. Though the mathematical treatment of this problem in its most simple approximated form leads to this difficult set of differential equations, it is not too difficult to see that the situation might physically correspond to an oscillatory phenomenon occurring after a threshold has been exceeded. Indeed, by raising the external concentration z in Figure 5 the permeability of II is increased since the function $h(z)$ is a monotone increasing function of z. As a consequence, the diffusion of potassium ions through layer II is increased. Therefore, y decreases and z increases initially. With decreasing y the difference between x and y increases so that the diffusion through I increases, lagging behind the increase of diffusion through II. The increased diffusion through I reduces x. Therefore, the difference between K_1 and x is increased. In this model K_1 and K_2 are supposed to be constant (the metabolic process keeping K_1 constantly higher than K_2 is not considered here). The increased difference $K_1 - x$ increases the diffusion in the inside layer which tends to restore the original value of x. At the same time the increase of z increases the diffusion in the outside layer, which decreases z again. Assuming the initial increase of z is large enough (corresponding to a threshold) and the time rates of the various diffusion processes are of the right order of magnitude, we see that it might be possible for the original situation to be restored after practically the whole content of the membrane of potassium ions has been released.

It has been found (Hodgkin and Huxley, 1947) that the charge carried by the potassium ions released in one impulse is about twice the charge on the resting membrane. If one assumes that the latter charge is located in a layer with a thickness of comparable order to that of the membrane, then the above observation is compatible with the mechanism under consideration.

Instead of treating here the set of equations (17), (18), and (19), we will consider first a simplified special case of it, which already shows some interesting features. We assume that the permeability of the membrane is determined by a similar type of mechanism. We again consider a CaP_2 layer as an essential element of the membrane. This compound of CaP_2 is in equilibrium with two complex ions CaP^+ and P^- according to:

$$CaP_2 \rightleftarrows CaP^+ + P^-, \tag{20}$$

$$CaP^+ \rightleftarrows Ca^{++} + P^-. \tag{21}$$

The equilibrium constants are, as before,

$$K_1 = \frac{(CaP_2)}{(CaP^+)\,(P^-)} \tag{22}$$

and

$$K_2 = \frac{(CaP^+)}{(Ca^{++})\,(P^-)}. \tag{23}$$

We will now consider also some electrical effects. An applied cathode (Fig. 6) will shift the equilibrium of reactions (20) and (21) toward the right-hand side, if we assume that the Ca^{++} ions are bound to relatively immobile P^- ions. This effect is due to the positive charge of the CaP^+ and Ca^{++} ions.

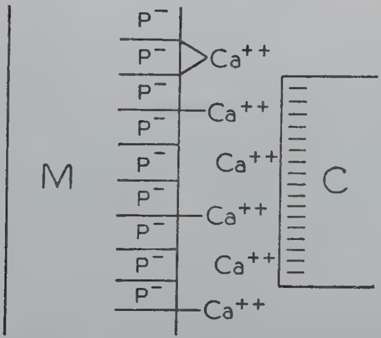

FIGURE 6. Membrane *M* in the neighborhood of an applied cathode *C* illustrating the effect of the attraction of the cathode on the Ca^{++} ions.

We may consider this effect as being due to the attraction of the Ca^{++} ions by the negative electrode. This effect might be expressed by the equation:

$$K_{i,V} = K_{i,0}\, e^{\frac{2\varepsilon}{kT} fV} \tag{24}$$

in which

$V =$ the electric potential difference across the CaP_2 layer.

$K_{i,V} =$ the equilibrium constant of the ith reaction (20) or (21) ($i = 1, 2$) when the electric potential difference across the CaP_2 layer is V. Similarly for $K_{i,0}$.

$\varepsilon =$ the charge of a monovalent ion.

$k =$ the Boltzmann constant.

$T =$ the absolute temperature.

$f =$ a correction factor which expresses the fact that the effective charge of the Ca^{++} ion might be less than 2 and the effective potential difference across the CaP_2 layer might be less than the measured potential difference. Therefore, f may describe the potential drop inside the membrane and across another layer. We will estimate the value of f later and expect it to be less than 1.

We suppose that the electric potential difference V is composed of the applied one (ΔV) and the diffusion potential of potassium. The latter has been assumed here because Osterhout (1949) has shown that it is a good approximation for the resting potential in the case of Nitella (cf. also Fleckenstein, 1942). We then find:

$$V = \frac{RT}{F} \log_e \frac{c_1}{c_2} + (\Delta V) , \tag{25}$$

c_1 and c_2 representing the concentrations of K^+ ions at both sides of the layer. Furthermore, it is assumed that the mobility of K^+ ions through the membrane is so much higher than that of any anions (cf. Osterhout, 1949) that the diffusion of the latter does not need to be taken into account in the calculation of the diffusion potential. Introducing (25) into (24) leads to:

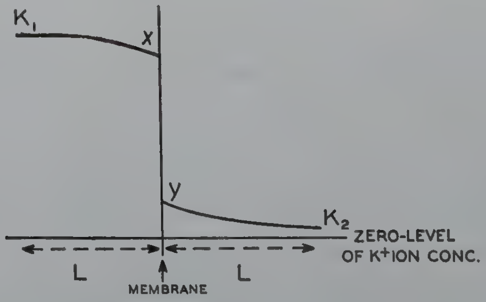

FIGURE 7. Schematic illustration of the concentration levels on both sides of a membrane of negligible thickness.

$$\boldsymbol{K}_{i,v}=\boldsymbol{K}_{i,0}\left(\frac{c_1}{c_2}\right)^{2f}e^{\frac{2\varepsilon}{kT}f(\Delta V)}. \tag{26}$$

As we see, the influence of the electric effects makes the reactions (20) and (21) of higher order.

To simplify matters in another respect, we will treat here first the case of a membrane whose thickness λ may be neglected. Then we have the situation shown in Figure 7.

The thickness of the diffusion layers on both sides of the membrane will be assumed to be the same as well as the diffusion constants of potassium in them. It will be shown, in a more general treatment below (cf. the last part of this paper), that these assumptions do not change anything significantly.

In the same way as above, the diffusion in the two layers next to the membrane with thickness L is found to be described by the following equations:

$$AL\frac{d\dfrac{K_1+x}{2}}{dt}=AD\frac{K_1-x}{L}-Ah(x-y), \tag{27}$$

$$AL\frac{d\dfrac{y+K_2}{2}}{dt}=Ah(x-y)-AD\frac{y-K_2}{L}. \tag{28}$$

In these equations the permeability h is considered to be a function of the potassium concentration inside the membrane. It will,

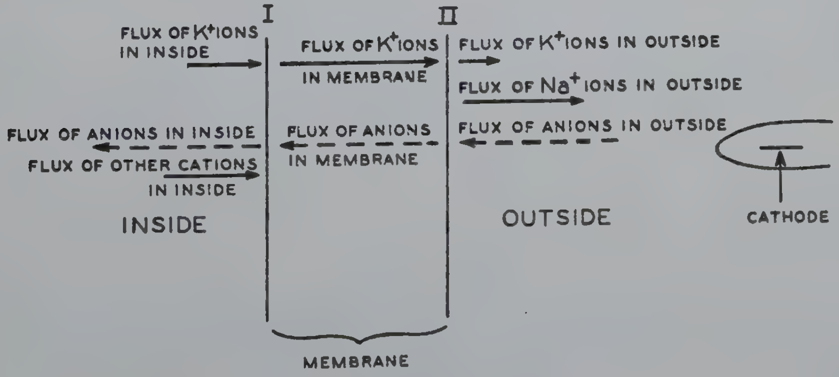
I
II
FLUX OF K⁺IONS IN INSIDE
FLUX OF K⁺IONS IN MEMBRANE
FLUX OF K⁺IONS IN OUTSIDE
FLUX OF Na⁺ IONS IN OUTSIDE
FLUX OF ANIONS IN INSIDE
FLUX OF ANIONS IN MEMBRANE
FLUX OF ANIONS IN OUTSIDE
FLUX OF OTHER CATIONS IN INSIDE
INSIDE
OUTSIDE
CATHODE
MEMBRANE

FIGURE 8

therefore, in general, be a function of x and y. However, because x is relatively high, the variations of x are relatively small. In addition, under our assumption that the membrane is permeable only to potassium ions, more of the latter will arrive at the external side of the membrane than leave there. This is because of the continuity of the electric current which inside the membrane is carried by potassium ions and by anions. We have so far neglected the latter for reasons of mathematical simplicity. In the outside layer, however, it is carried for the most part by sodium ions and anions (Fig. 8).

Therefore, the accumulation of K^+ ions will take place at the external side II of the membrane. This is another reason why the permeability is determined to a large extent by y in Figure 7.

However it will be shown later on how the more general case, in which the permeability is also dependent on x, can be treated approximately.

Introducing $h = h(y)$ into the equations (27) and (28) and simplifying the latter equations, we get:

$$\frac{dx}{dt} = \frac{2D}{L^2}(K_1 - x) - \frac{2h(y)}{L}(x - y), \tag{29}$$

$$\frac{dy}{dt} = \frac{2h(y)}{L}(x - y) - \frac{2D}{L^2}(y - K_2). \tag{30}$$

Because h is considered here to be a function of one of the dependent variables, this set of differential equations is also nonlinear. A set of this kind might be considered as a first extension of the usual equations describing diffusion phenomena (including permeability features) with constant diffusion and permeability coefficients, as has been done in most cases up to the present time (Rashevsky, 1948; see also for discussion of some nonlinear diffusion cases).

Addition of the two equations (29) and (30) gives

$$\frac{d(x+y)}{dt} = \frac{2D}{L^2}(K_1 + K_2) - \frac{2D}{L^2}(x + y). \tag{31}$$

The solution of (31) is:

$$x + y = e^{-\frac{2D}{L^2}t} \left\{ (x+y)_0 + \int_0^t e^{-\frac{2D}{L^2}t} \frac{2D}{L^2}(K_1 + K_2)\,dt \right\},$$

or

$$x + y = (K_1 + K_2) + e^{-\frac{2D}{L^2}t} \{(x + y)_0 - (K_1 + K_2)\}, \tag{32}$$

$(x + y)_0$ being the initial value of $(x + y)$.

Hence in the steady state (for $t \to \infty$) we have:

$$x + y = K_1 + K_2, \tag{33}$$

as could have been obtained also directly from (31).

Solving for x from (33), we get:

$$x = (K_1 + K_2) - y. \tag{34}$$

Subtraction of equation (30) from (29) gives:

$$\frac{d(x-y)}{dt} = \frac{2D}{L^2}(K_1 - K_2) - \frac{2D}{L^2}(x-y) - \frac{4h(y)}{L}(x-y). \tag{35}$$

To calculate $h(y)$ we will first make the very crude assumption that $f \approx 1$ in (26). For c_1 and c_2 in (26) we take x and y respectively as in Figure 7. Then we find from (26):

$$K_{i,V} = K_{i,0} \left(\frac{x}{y} \right)^2 e^{\frac{2\varepsilon}{kT}(\Delta V)}. \tag{36}$$

Since

$$y << K_1,$$

and hence

$$y << K_1 + K_2,$$

therefore we may write:

$$x \approx K_1 + K_2. \tag{37}$$

Hence in this approximation, x may be taken as constant, as could have been concluded from our above considerations in connection with the relatively insignificant variations of x.

We now introduce the following notations:

$$K_1 + K_2 = 2\bar{\Delta}, \tag{38}$$

$$K_1 - K_2 = 2\bar{\varepsilon}. \tag{39}$$

Then we find from (36), together with (37) and (38),

$$K_{i,V} = 4K_{i,0}\,\bar{\Delta}^2\, e^{\frac{2\varepsilon}{kT}(\Delta V)}\, y^{-2}. \tag{40}$$

From (22) and (23), in which we now take $K_{i,V}$ instead of K_i, we obtain:

$$(\mathrm{CaP_2}) = K_{1,V} (\mathrm{CaP^+}) (\mathrm{P^-}), \tag{41}$$

$$(\mathrm{CaP^+}) = K_{2,V} (\mathrm{Ca^{++}}) (\mathrm{P^-}). \tag{42}$$

Introducing (42) into (41) we find

$$(\mathrm{CaP_2}) = K_{1,V} K_{2,V} (\mathrm{Ca^{++}}) (\mathrm{P^-})^2. \tag{43}$$

We now have the following expression for the reaction system (20) and (21), which is similar to equation (8):

$$2(\mathrm{CaP_2}) + (\mathrm{CaP^+}) + (\mathrm{P^-}) = P_0. \tag{44}$$

Introducing (40) into (41) and (43), and then the latter into (44) we obtain:

$$\begin{aligned} &32 K_{1,0} K_{2,0} \bar{\Delta}^4 e^{\frac{4\varepsilon}{kT}(\Delta V)} (\mathrm{Ca^{++}}) \left(\frac{\mathrm{P^-}}{y^2} \right)^2 \\ &+ 4 K_{2,0} \bar{\Delta}^2 e^{\frac{2\varepsilon}{kT}(\Delta V)} (\mathrm{Ca^{++}}) \frac{\mathrm{P^-}}{y^2} + (\mathrm{P^-}) - P_0 = 0. \end{aligned} \tag{45}$$

Similar to assumption (10), we assume that in the case of reactions (20)—(21) we have:

$$a\, h = (\mathrm{P^-}). \tag{46}$$

Elimination of $(\mathrm{P^-})$ from (45) and (46) yields the following equation for h:

$$\begin{aligned} &32 K_{1,0} K_{2,0} \bar{\Delta}^4 e^{\frac{4\varepsilon}{kT}(\Delta V)} (\mathrm{Ca^{++}}) a^2 \left(\frac{h}{y^2} \right)^2 \\ &+ 4 K_{2,0} \bar{\Delta}^2 e^{\frac{2\varepsilon}{kT}(\Delta V)} (\mathrm{Ca^{++}}) a \frac{h}{y^2} + a\, h - P_0 = 0. \end{aligned} \tag{47}$$

We will now first show that the term $a\, h$ may be neglected. To do this we have to find plausible estimates for the various parameters. F. C. McLean and A. B. Hastings (1935) find for body fluids:

$$K_{1,0} K_{2,0} \approx 10^3 — 10^4. \tag{48}$$

Because we might expect $K_{1,0} << K_{2,0}$ (secondary ionizations usually being "weaker" than primary ones), we estimate

$$K_{2,0} \sim 10^2\text{—}10^3. \tag{49}$$

According to Webb and Young (1940) and R. S. Bear and F. O. Schmidt (1939) we have the following orders of magnitude:

$$(K_1) = 3.10^{-1}\ \mathrm{M/l}\,, \tag{50}$$

$$(K_2) = 10^{-2}\ \mathrm{M/l}\,. \tag{51}$$

Taking as an estimate of (Ca^{++}) the value of that concentration in Ringer's solution we find that the order of magnitude is (Fulton-Howell, 1946):

$$(Ca^{++}) \sim 10^{-3}\ \mathrm{M/l}\,. \tag{52}$$

From (38), (50), and (51) we find:

$$\bar{\Delta} = \frac{K_1 + K_2}{2} = 0.16\ \mathrm{M/l}. \tag{53}$$

Taking $(\Delta V) = 0$ (no electric field applied), using (49) and (51) and keeping in mind that y is of the order of magnitude of K_2, we find for the coefficient of h in the second term in (47):

$$4.10^2\ (0.16)^2 \cdot 10^{-3}\ (0.01)^{-2}\ \alpha \approx 10^2\ \alpha\,,$$

which is large compared with the coefficient α of h in the third term. We will, therefore, neglect the third term in (47). Equation (47) now takes the form:

$$a_1 \left(\frac{h}{y^2} \right)^2 + b_1 \left(\frac{h}{y^2} \right) - P_0 = 0 \tag{54}$$

with

$$a_1 = 32 K_{1,0} K_{2,0}\, \bar{\Delta}^4\, e^{\frac{4\varepsilon}{kT}(\Delta V)}\ (Ca^{++})\, \alpha^2 \tag{55}$$

and

$$b_1 = 4 K_{2,0}\, \bar{\Delta}^2\, e^{\frac{2\varepsilon}{kT}(\Delta V)}\ (Ca^{++})\, \alpha\,. \tag{56}$$

The solution of (54) is given by

$$\frac{h}{y^2} = \frac{-b_1 + \sqrt{b_1^2 + 4a_1 P_0}}{2a_1}, \tag{57}$$

or

$$h = \beta\, y^2 \tag{58}$$

with

$$\beta = -\frac{b_1}{2a_1} + \sqrt{\left(-\frac{b_1}{2a_1}\right)^2 + \frac{P_0}{a_1}}. \tag{59}$$

If we again assume as above that the conductance is a measure of the ionic permeability we may compare the theoretically derived result (58) with the observation of Hodgkin (1947) who found that the conductance was increased roughly three-fold when the external potassium concentration was trebled. However, Hodgkin states that there is much scatter in the experimental results and he considers his estimate to be crude. The fact that this investigator also found that the conductance was reduced to about one-half by removal of potassium would suggest that a term h_0, independent of y, should be added to the right-hand side of (58). This term has been omitted in our considerations for reasons of mathematical simplicity. In addition, our formulae (58) and (62) predict a definite dependence of this relation of the conductance and the external potassium concentration on the Ca^{++} ion concentration and on an applied external electrical field. It would be interesting to compare these predictions with experimental data as soon as they are available to obtain some additional ideas for the improvement of this very crude theory.

From (55) and (56) we have

$$-\frac{b_1}{2a_1} = -\frac{1}{16K_{1,0}\,\bar{\Delta}^2\, e^{\frac{2\varepsilon}{kT}(\Delta V)}\,\alpha}; \tag{60}$$

$$\frac{P_0}{a_1} = \frac{P_0}{32K_{1,0}K_{2,0}\,\bar{\Delta}^4\, e^{\frac{4\varepsilon}{kT}(\Delta V)}\,(Ca^{++})\,\alpha^2}. \tag{61}$$

Substitution of (60) and (61) into (59) leads us to:

$$\beta = \left\{-1 + \sqrt{1 + \frac{8K_1P_0}{K_2(Ca^{++})}}\right\} \frac{1}{16K_1\alpha}\,\frac{e^{-\frac{2\varepsilon}{kT}(\Delta V)}}{\vec{\Delta}^2}, \tag{62}$$

in which the index 0 has been omitted from the K's. From (58) we see that h plotted as a function of the potassium concentration y gives a parabola (Fig. 9). From (58) and (62) we see that the permeability h decreases with increasing positive applied potential difference (ΔV), while h increases with increasing negative applied potential difference (ΔV). Furthermore, h decreases with increasing (Ca^{++}), while h increases with increasing y, the potassium ion concentration just outside the membrane. All these qualitative conclusions are in agreement with experimental evidence (R. S. Lillie, 1924; Höber, 1945).

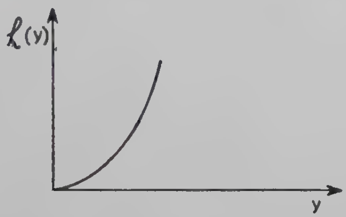

FIGURE 9. Permeability to potassium ions as a function of the potassium concentration just outside the membrane according to equation (58).

Substitution of (39) and (58) into (35) gives

$$\frac{d(x-y)}{dt} = k\,2\bar{\varepsilon} - k(x-y) - \frac{4\beta}{L} y^2 (x-y)\,, \tag{63}$$

where

$$k = \frac{2D}{L^2}. \tag{64}$$

For simplification of notation let us write

$$\frac{4\beta}{L} = \gamma\,, \tag{65}$$

and introduce as new variables

$$\frac{x+y}{2} = u\,, \tag{66}$$

$$\frac{x-y}{2} = v\,, \tag{67}$$

so that

$$x = u + v \tag{68}$$

and

$$y = u - v. \tag{69}$$

From (66), (33) and (38) we then have:

$$u \approx \bar{\Delta}. \tag{70}$$

Introduction of (65), (67), (69) and (70) into (63) yields:

$$\frac{dv}{dt} = k\bar{\varepsilon} - kv - \gamma(\bar{\Delta} - v)^2 v. \tag{71}$$

Rearranging (71) and putting

$$\frac{v}{\bar{\Delta}} = \xi, \tag{72}$$

$$\frac{\bar{\varepsilon}}{\bar{\Delta}} = z, \tag{73}$$

we find:

$$\frac{d\xi}{dt} = k\{z - (1+\delta)\xi + 2\delta\xi^2 - \delta\xi^3\}, \tag{74}$$

where

$$\delta = \frac{\gamma \Delta^2}{k} \tag{75}$$

is a dimensionless constant, and z now has a new meaning.

Denoting the right-hand side of (74) by $kF(\xi)$, so that

$$F(\xi) \equiv z - (1+\delta)\xi + 2\delta\xi^2 - \delta\xi^3, \tag{76}$$

we have:

$$\frac{d\xi}{dt} = kF(\xi). \tag{77}$$

Because $x \geqslant 0$ and $y \geqslant 0$, we see from (33), (66) and (67) that v and, therefore, according to (72), ξ, is as great as possible if x is as large as possible and y as small as possible. Physiologically this occurs [$(x+y)/2 = u$ being constant according to (33)] when

$$y = 0. \tag{78}$$

Accordingly, using (66), (70), and (78) we find

$$x = 2\Delta. \tag{79}$$

This means, according to (38), $x = K_1 + K_2 > K_1$.

Therefore, we see from (67), (78), and (79) that the maximum value of v is

$$v = \bar{\Delta}, \tag{80}$$

and that of ξ, according to (72), is

$$\xi = 1 . \tag{81}$$

We now find from (76) that

$$\begin{aligned} F(0) &= z > 0 , \\ F(1) &= z - 1 < 0 . \end{aligned}$$

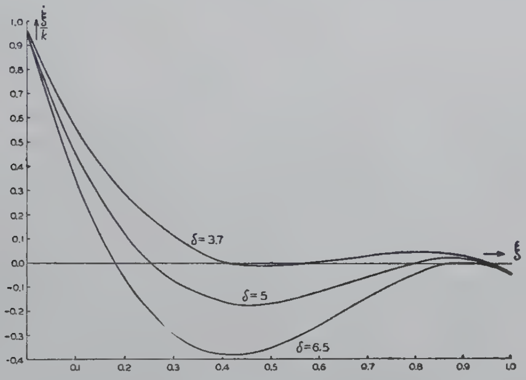

FIGURE 10. Illustration of the relation between $\frac{\dot{\xi}}{k}$ and ξ for $K_1 = 50$ and $K_2 = 1$ mM/l and for several values of δ. The permeability is given by (58) and (62).

A plausible value of z is 0.96. According to (50) and (51), we have $z = 0.94$, while in experiments on Nitella $z = 0.96$ (Osterhout, 1949). The function $F(\xi)$ has been plotted against ξ for $z = 0.96$ and for several values of the parameter δ in Figure 10. If

$$3.65 \leq \delta \leq 6.85 , \tag{82}$$

then $F(\xi)$ has three roots in the interval $0 \leq \xi \leq 1$. Therefore, we see that there are three equilibrium values of ξ and hence of x and y also. As it can easily be seen from (74) or from Figure 10, the smallest root of $F(\xi)$ corresponds to a stable equilibrium, the next larger one to an unstable equilibrium, and the largest one again to a stable equilibrium. As an illustration, we find that for $\delta = 5$, $K_1 = 0.050$ M/l, and $K_2 = 0.001$ M/l (Osterhout, 1949), these roots are

$$\xi_1 = 0.254 \text{ corresponding to } y_1 = 0.019 \text{ and } x_1 = 0.032\,, \tag{83}$$

$$\xi_2 = 0.800 \quad \text{''} \quad \text{''} \quad y_2 = 0.005 \quad \text{''} \quad x_2 = 0.046\,, \tag{84}$$

$$\xi_3 = 0.946 \quad \text{''} \quad \text{''} \quad y_3 = 0.0014 \quad \text{''} \quad x_3 = 0.050\,. \tag{85}$$

The value y_3 gives the potassium ion concentration in M/l just outside the membrane in the original state. Adding slightly more potassium than $y_2 - y_3 = 0.0036$ (M/l) just outside the membrane does change the equilibrium state into $y_1 = 0.019$ (M/l). As we see here, $y_2 - y_3$ corresponds to a threshold of chemical stimulation through the local addition of potassium outside the membrane. We find here a value of the right order of magnitude (Hill and Osterhout, 1937). Because of the very crude assumptions which we have made, particularly the assumption of $f = 1$ in (26), we can hardly expect more than agreement of the orders of magnitude, and it is not worthwhile to go into the details here. However, at this stage we can estimate the value of f. As we have seen above, increasing the (Ca^{++}) decreases β according to (62) and, therefore, also, according to (65) and (75), δ. As we see from Figure 10 decreasing δ moves the two smaller roots toward each other until they coincide. At the same time the distance between the two larger roots, corresponding to the threshold, increases. For still smaller values of δ than that one which corresponds to the coincidence of the two smallest roots, there remains only the largest root corresponding to the original state. This dependence of the threshold on the (Ca^{++}) might correspond to the experimentally observed increase of threshold (or decreased irritability) upon adding Ca^{++} ions (R. S. Lillie, 1923; Höber, 1945). Also, the original state might be restored (cf. Osterhout, 1933 for a restoration of irritability by adding $CaCl_2$ solution). Adding more Ca^{++} than corresponds to the smallest value of δ, for which there are still three roots, might also lead to Ca narcosis. The quantity β increases with increasing applied negative potential difference, as is seen from (62). Therefore, according to (65) and (75), δ also increases. Hence this mechanism also gives parametric electrical stimulation by an applied cathode. To estimate f we will consider the case in which δ is changed in such a way that starting with the situation $\delta = 3.65$ in which the two smaller roots coincide we arrive at the situation $\delta = 6.85$ in which the two larger roots coincide. The latter corresponds to zero threshold. We have then, from (62),

$$e^{-\frac{2\varepsilon}{kT} f(\Delta V)} = \frac{6.85}{3.65}. \tag{86}$$

From the known values of ε and k, taking $T = 300°K$, we find:

$$f(\Delta V)_{\mathrm{mV}} = -8 .$$

Assuming that $(\Delta V)_{\mathrm{mV}} = -10$, which is experimentally of the right order of magnitude (Cole and Curtis, 1940), we find

$$f = 0.8 . \tag{87}$$

Though higher than we might have expected, we find a value of f which is less than 1 for a reasonable value of the electrical threshold.

Using this value of f we find for the "resting potential" which corresponds to the original state, according to (85), a potential difference of the order

$$58(0.8) \log \frac{50 \times 10^{-3}}{14 \times 10^{-4}} = 72(\mathrm{mV}) , \tag{88}$$

which is of the right order of magnitude (Osterhout, 1949).

Similarly, we may make an estimate of the "action potential." From equations (83) and (85) we find the value

$$58(0.8) \left(\log \frac{32 \times 10^{-3}}{19 \times 10^{-3}} - \log \frac{50 \times 10^{-3}}{14 \times 10^{-4}} \right) = -59(\mathrm{mV}) , \tag{89}$$

which is also of the correct order of magnitude (Hill and Osterhout, 1934). This would correspond to the depolarization of the membrane.

Furthermore, the permeability increase corresponding to the transition from the original state to the final state is, according to (58), (83), and (85),

$$\left(\frac{19 \times 10^{-3}}{14 \times 10^{-4}} \right)^2 \approx 200 . \tag{90}$$

This is also the right order of magnitude (Cole and Curtis, 1938). However, it should be realized here that this is only a very crude result; the range of validity of our approximation should be investigated. Particularly, the neglect of the third term in (47) is no longer justified; however, the order of magnitude probably does not change significantly due to this approximation.

It might be interesting to show here a possible way in which the one-factor theory may be obtained from the above considerations.

We shall show this also as an example for the particular case

$\delta = 5$. From the curve in Figure 10, corresponding to this value, we have the equation

$$\dot{\xi} = k(0.96 - 6\,\xi + 10\,\xi^2 - 5\,\xi^3)$$

or

$$\dot{\xi} = -5k(\xi - 0.254)\,(\xi - 0.800)\,(\xi - 0.946)\,. \qquad (91)$$

We then have for the slope at the value $\xi = 0.946$, corresponding to the original equilibrium state,

$$\left(\frac{d\,\dot{\xi}}{d\,\xi}\right)_{\xi=0.946} = -\,0.5k\,.$$

Therefore, approximating the curve given by (91) by its tangent at the point $(0.946\,,\,0)$, we have from Taylor's theorem, keeping only terms linear in ξ:

$$\dot{\xi} = \dot{\xi}_{\text{init.}} - 0.5k(\xi - 0.946)\,. \qquad (92)$$

The initial value of ξ, $\xi_{\text{init.}}$, due to stimulus or "impulse," is

$$\dot{\xi}_{\text{init.}} = \int_0^t \ddot{\xi}\,dt = C\,, \qquad (93)$$

where C is a constant, which, however, depends on the time course of the stimulus.

Substituting into (92) for ξ its value from (72) and (67), using

$$\dot{\xi} = \frac{\dot{x} - \dot{y}}{2\,\Delta}\,,$$

and keeping in mind that according to our approximation (33)

$$\dot{x} + \dot{y} = 0\,,$$

we find:

$$\dot{y} = C_1 - 0.5k(y - 0.0014)\,, \qquad (94)$$

where C_1 is proportional to C and 0.0014 M/l is the value of y in the original equilibrium state. From (94) we see that our k turns out to have the order of magnitude of the time factor of the one-factor theory.

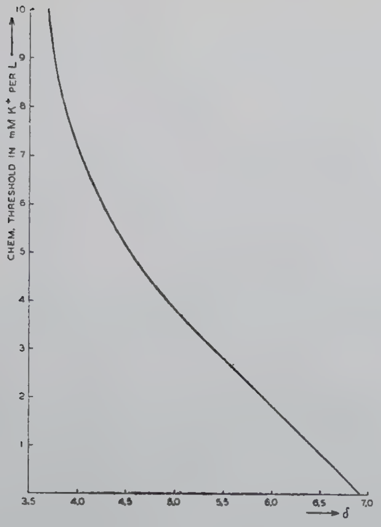

FIGURE 11. Chemical threshold of (K+) in mM/l as a function of the parameter δ for the case $K_1 = 50$ and $K_2 = 1$ mM/l.

The threshold can be determined as a function of δ from the curves in Figure 10. The relation obtained is plotted in Figure 11. From this curve and equations (62), (65), and (75) we can obtain the dependence of this (chemical) threshold on the Ca^{++} ion concentration and on the applied (ΔV). Assuming $(\Delta V) = 0$ and $\delta = 3.65$ we obtain in the above outlined way:

(Ca^{++}) in fractions of $(Ca^{++})_n$	Chem. Threshold in mM/l (K^+)
0.285	0.00
0.300	0.50
0.333	1.20
0.400	2.25
0.500	3.50
0.600	4.50
0.667	5.20
0.833	7.20
0.900	8.00
1.000	10.00

This relation between the chemical threshold and (Ca^{++}) is shown in Figure 12 in which the curve for $\delta = 5$ has also been drawn.

In a similar way, which has also been outlined above, we can

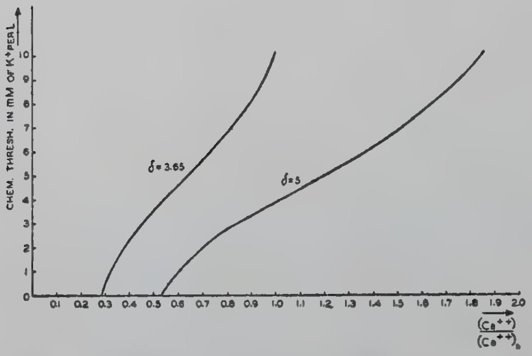

FIGURE 12. Chemical threshold of (K^+) in mM/l as a function of $(Ca^{++})/(Ca^{++})_n$ for $K_1 = 50$ and $K_2 = 1$ mM/l.
Two curves are shown, one for the initial value 3.65 for the parameter δ (corresponding to Ca^{++} "narcosis") and the other for the initial value 5 of that parameter. $(Ca^{++})_n$ is the value of (Ca^{++}) corresponding to those values of δ. To simplify the calculations we have chosen for $8K_1P_0 >> K_2$.

calculate the dependence of the threshold of chemical stimulation on the applied field (ΔV) which gives us the following table if we assume the electrical threshold to be —5 mV:

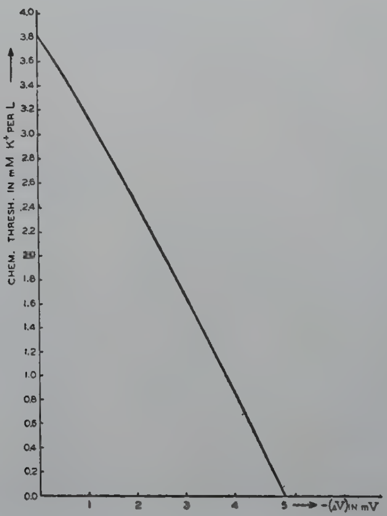

FIGURE 13. Chemical threshold of (K^+) in mM/l as a function of an applied voltage for $K_1 = 50$, $K_2 = 1$ mM/l, $\delta_n = 5$. The symbol δ_n denotes the value of the parameter δ when $(\Delta V) = 0$. The electrical threshold is taken to be — 5 mV.

(ΔV) (in mV)	Chem. Threshold in mM/l K+
0	3.80
—1	3.15
—2	2.42
—3	1.66
—4	0.86
—5	0.00

This relation between the threshold and (ΔV) is shown in Figure 13.

It would be interesting to compare these results with experimental data. As far as we know these are not yet available. The electrical threshold can be expressed as a function of the Ca++ ion concentration. From (62), (65), and (75), we find, after some simple rearrangements:

$$\frac{2\varepsilon}{kT} f(\Delta V)_{\substack{\text{thr} \\ (\text{Ca}^{++})}} = \frac{2\varepsilon}{kT} f(\Delta V)_{\substack{\text{thr} \\ \text{n}}} + \log_e \frac{-1 + \sqrt{1 + \dfrac{C}{(\text{Ca}^{++})}}}{-1 + \sqrt{1 + \dfrac{C}{(\text{Ca}^{++})_\text{n}}}}, \quad (95)$$

in which $(\Delta V)_{\substack{\text{thr} \\ (\text{Ca}^{++})}}$ is the electrical threshold corresponding to the particular (Ca++) ion concentration, while $(\Delta V)_{\substack{\text{thr} \\ \text{n}}}$ and $(\text{Ca}^{++})_\text{n}$ are the corresponding normal (or, as we may assume, initial) values, and C is a constant equal to

$$\left(\frac{8K_1P_0}{K_2}\right).$$

We can then determine $(\Delta V)_{\substack{\text{thr} \\ \text{n}}}$ from:

$$6.85 = \delta_0 \, e^{-\frac{2\varepsilon}{kT} f(\Delta V)_{\substack{\text{thr} \\ \text{n}}}}, \quad (96)$$

δ_0 being the initial value of δ.

Taking as a plausible value of $\delta_0 = 5$ we find, with $f = 0.8$, $(\Delta V)_{\substack{\text{thr} \\ \text{n}}} = -5$ mV.

We then obtain from (95) the ratio

$$\frac{(\Delta V)_{\mathrm{thr}\,(\mathrm{Ca}^{++})}}{(\Delta V)_{\mathrm{thr}\,\mathrm{n}}}$$

as a function of (Ca^{++}). The graph of this function (Fig. 14) may be compared with the corresponding one of F. Brink and others (1946). Though the trend is correct, our range of (Ca^{++}) values in which the threshold changes from 0 to its normal value is much smaller than the one found experimentally. This might perhaps be explained by the fact that local stimulation may be more sensitive than general stimulation or that we have not considered any accommodation effects. The discrepancy is, however, probably due to the crudeness of the theory e.g., the neglect of permeability of Ca^{++} ions and of diffusion potential of Ca^{++} ions.

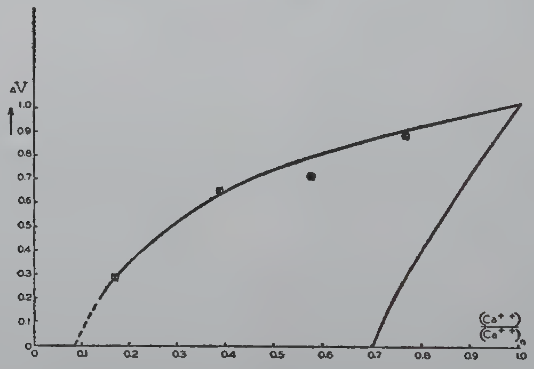

FIGURE 14. Electrical threshold expressed in fractions of its initial value as a function of the ratio $(\mathrm{Ca}^{++})/(\mathrm{Ca}^{++})_{\mathrm{n}}$ for the initial value $\delta_0 = 5$, $K_1 = 50$ mM/l and $K_2 = 1$ mM/l. The initial or normal value $(\mathrm{Ca}^{++})_{\mathrm{n}}$ of (Ca^{++}) corresponds to δ_0 and the normal threshold. In the same graph the experimental values, indicated by x and an experimental curve (Brink and others, 1946) are shown.

Unfortunately, the duration of the "action potential" given by the integral

$$5kt = \int_{0.8}^{0.254} \frac{d\xi}{(\xi - 0.254)(\xi - 0.800)(\xi - 0.946)} \tag{97}$$

for the case $\delta = 5$ is much too large. A slight overshoot of the unstable root 0.8 had to be taken to keep t finite. However, the integral in (97) remains infinite as long as 0.254 is taken as the upper limit. Therefore, the latter also must be slightly shifted. Presumably a recovery process takes place which is superimposed on the considered process and keeps t finite. The infinite value of t, as obtained from (97), is due to the fact that $\dot{\xi} = 0$ at the roots. A similar phenomenon is discussed by Rashevsky (1948, p. 347) in the two-factor theory of conduction.

Another interesting dependence of the threshold is that on K_2, the level of the external potassium concentration. This, however, will be postponed until after a more general analytical treatment is given below. Qualitatively it can be seen already, however, that an increase of K_2, which decreases the quantity

$$z = \frac{K_1 - K_2}{K_1 + K_2},$$

shifts all the curves in Figure 10 toward smaller values of the ordinates. It, also, therefore, decreases the difference of the two largest roots of $F(\xi)$, (the threshold), which is in agreement with experimental evidence (Höber, 1945).

On the basis of the value 0.8 for f we can estimate the electrical field strength corresponding to an applied electrical potential difference of $-$ 10 mV. Even if we assume the latter across a distance of 1 Å we find 8×10^5 V/cm for the field strength. This does not compare too unfavorably with an estimate of Osterhout (1934) of 2×10^4 V/mm or more. It would be only slightly worse in this respect for $f = 1$. We see that this model gives some results which are in agreement with experimental facts, at least as far as the order of magnitude is concerned. It is interesting to point out that these results, which give absolute values, were obtained by using the absolute value of the unit electric charge and the Boltzmann constant. However, the fact that the value of f is found to be different from unity indicates that a more general treatment is necessary. The power of y in (58) should be made equal to $nf = p$ instead of 2 where n is the charge of the ion bound to the P^- ion. We have hitherto identified this ion with Ca^{++}. To illustrate this more general treatment and to make some use of it, we proceed as follows. Taking, instead of (58),

$$h = \beta y^p, \tag{98}$$

we obtain, instead of (74), in the same way as before:

$$\dot{\xi} = k\{z - \xi - \beta(1 - \xi)^p \xi\}, \tag{99}$$

where the parameters k, z, and β have the same meaning as above, cf. (64), (73), and (62) respectively.

Putting, as before,

$$G(\xi) \equiv \frac{\dot{\xi}}{k} = z - \xi - \beta(1-\xi)^p \xi, \tag{100}$$

we will determine here as functions of p the critical values β_1 and β_2 of β for which the two smaller roots in Figure 15 and the two larger roots respectively coincide. These values of β have given us before, for the case $p = 2$, the order of magnitude of the electrical threshold.

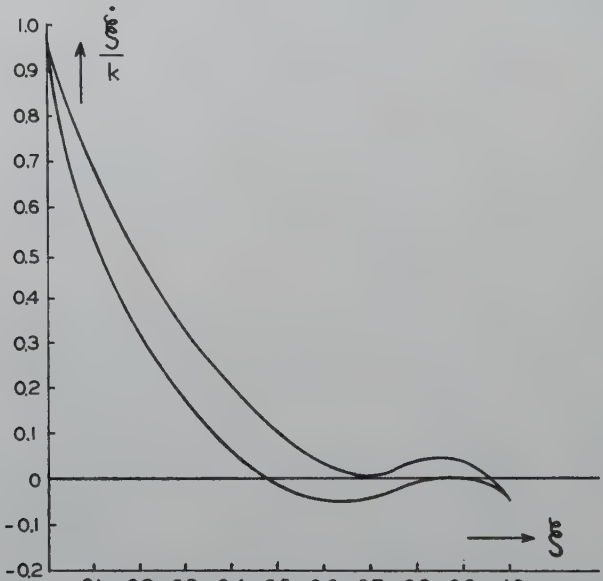

FIGURE 15

Introducing as a new independent variable

$$\eta = 1 - \xi, \tag{101}$$

we have

$$\begin{aligned} G(\xi) \equiv H(\eta) &\equiv z - 1 + \eta - \beta\,\eta^p(1-\eta) \\ &\equiv -\mathbf{e} + \eta - \beta\,\eta^p + \beta\,\eta^{p+1} \end{aligned} \tag{102}$$

in which

$$\mathbf{e} = 1 - z. \tag{103}$$

The curves

$$\dot{\xi} = kG(\xi)$$

or

$$\dot{\eta} = -kH(\eta)$$

are tangent to the ξ or η axis respectively, if:

$$H(\eta) = 0 \tag{104}$$

and

$$H'(\eta) \equiv 1 - p\,\beta\,\eta^{p-1} + (p+1)\beta\,\eta^{p} = 0\,. \tag{105}$$

The latter leads to:

$$\beta = \frac{1}{p\,\eta^{p-1} - (p+1)\,\eta^{p}}. \tag{106}$$

Substitution of (106) into (104) yields the following quadratic equation in η using (102):

$$p\,\eta^2 - \eta\,\{\mathbf{e}(p+1) + (p-1)\} + \mathbf{e}p = 0 \tag{107}$$

the solution of which is:

$$\eta_{1,2} = \frac{\mathbf{e}(p+1) + (p-1) \pm \sqrt{\{\mathbf{e}(p+1) + (p-1)\}^2 - 4\mathbf{e}p^2}}{2p}. \tag{108}$$

It can easily be seen that the expression under the sign of the radical,

$$(p+1)^2\,\mathbf{e}^2 - 2(p^2+1)\,\mathbf{e} + (p-1)^2 \geqslant 0$$

if

$$\mathbf{e} \leqslant \frac{(p-1)^2}{(p+1)^2}. \tag{109}$$

From (106) and (108) we find the critical values β_1 and β_2 for which we are looking.

In this way the quantities β_1 and β_2 and, therefore, of

$$\frac{\beta_2}{\beta_1} = \frac{\delta_2}{\delta_1},$$

can be expressed as functions of e and p. Because, according to (103), (73), (39), and (38),

$$\mathbf{e} = 1 - z = \frac{2K_2}{K_1 + K_2}$$

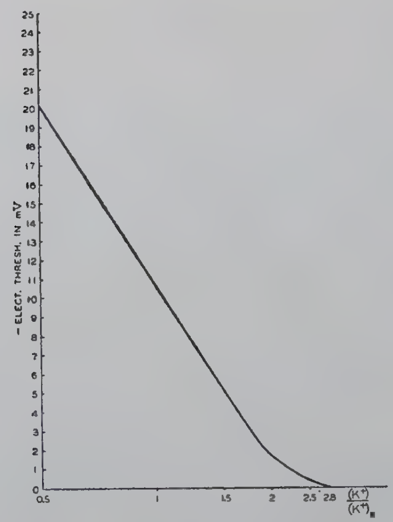

FIGURE 16. The negative of the electrical threshold as a function of $(K_2^+)/(K_2^+)_n$. For reasons of mathematical simplicity it is assumed that the original state corresponds to "narcosis." $K_1 = 50$ mM/l $(K_2^+)_n$ was actually taken in this illustration equal to 1 mM/l. $(K_2^+)/(K_2^+)_n$ has been plotted on a logarithmic scale.

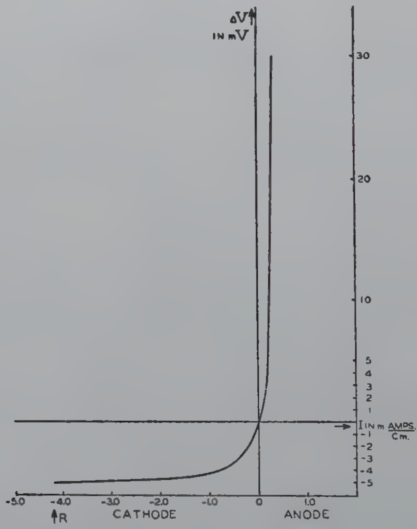

FIGURE 17. Applied potential (ΔV) vs. membrane current intensity I. In order to make these calculations it was necessary to assume that the permeability approached 1/7 of its normal value [when $(\Delta V) = 0$] for small K^+ ion concentration and that in series with the membrane there is an additional resistance 1/12 of that due to the resistance of the normal membrane.

we can calculate in this way $\frac{\delta_2}{\delta_1}$ and, therefore (ΔV) as a function of K_2 for a fixed value of p, e.g., $p=2$, and for a fixed value of K_1, using the relation

$$e^{-\frac{2\varepsilon}{kT}f(\Delta V)} = \frac{\delta_2}{\delta_1}, \tag{110}$$

obtained from (62) together with (65) and (75). The result of this calculation for $K_1 = 0.050$ M/l is shown in the following table: The calculations were made for a Ca^{++} concentration which corresponds to calcium "narcosis." This particular case was chosen only as an illustration.

K_2 (in M/l)	$-(\Delta V)$ (in mV)
0.0005	20.1
0.0010	10.4
0.0015	5.3
0.0020	1.7
0.0025	0.6
0.0028	0.0

where f is again taken as 0.8.

This relation is shown in Figure 16.*

Furthermore, we can derive from (62) and (58) the permeability h and, therefore, the resistance for negative as well as positive (ΔV) (Fig. 17). This may be compared with Figure 5 of K. S. Cole and H. J. Curtis (1940). The difference may be explained by the fact that we have neglected accommodation effects. On the other hand, it might be interesting to point out here that in principle our formulae predict influences of (Ca^{++}) and K_2 on these rectification curves.

We shall show here how in principle the so-called time-course of the excitatory disturbance and "local non-conducted response" (Katz, 1937) can be obtained from our mechanism. To illustrate this let us again take, only as an example, the curve in Figure 10 for $\delta = 5$, which is given by equation (91).

Denoting by

$$\zeta = -(\xi - 0.946) \tag{111}$$

we find from (91)

---

*The linear relation between the electrical threshold and the external potassium ion concentration for low K_2 has recently been observed by Howard Jenerick (personal communication).

$$-\dot{\zeta} = +5k(0.692-\zeta)(0.146-\zeta)\zeta\,. \tag{112}$$

The graph of $\dot{\zeta}$ given by (112) against ζ as shown in Figure 18a.

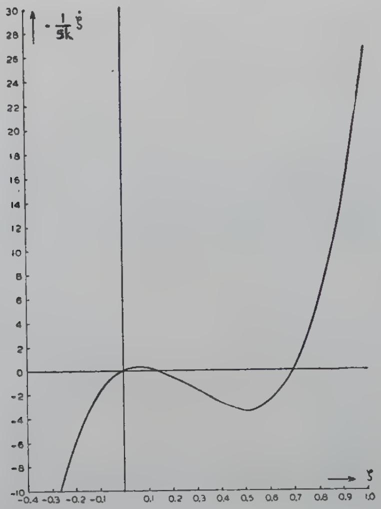

FIGURE 18a. The "local phenomenological characteristic" for $K_1 = 50$ mM/l, $K_2 = 1$ mM/l and $\delta = 5$.

This corresponds to the "local phenomenological characteristic" of Weinberg (1942). Weinberg's instantaneous time constant, k, is plotted in Figure 18b:

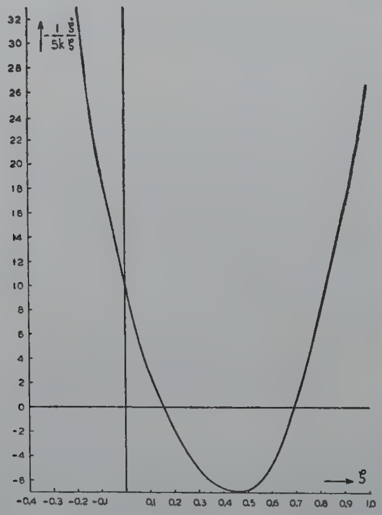

FIGURE 18b. The "instantaneous time constant" for $K_1 = 50$, $K_2 = 1$ mM/l and $\delta = 5$.

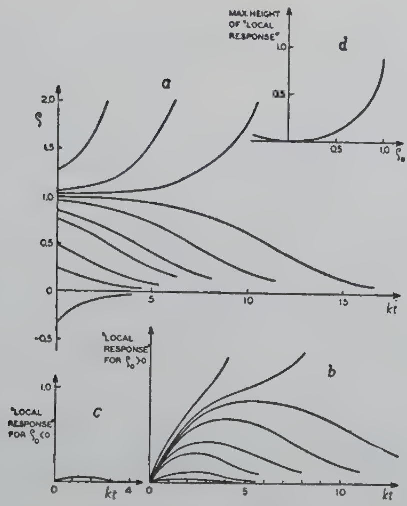

FIGURE 19. a. Graph of standardized excitability $\rho = \frac{\zeta}{0.146}$ as a function of kt. b. "Local response" for positive initial disturbance ρ_0 as a function of kt. c. "Local response" for negative initial disturbance ρ_0 as a function of kt. d. Maximum height of the "local response" as a function of ρ_0. This figure is based on $K_1 = 50$ mM/l, $K_2 = 1$ mM/l and $\delta = 5$.

$$k = -\frac{\dot{\zeta}}{\zeta} = 5k(0.146 - \zeta)(0.692 - \zeta). \tag{113}$$

Integration of (112) leads us to:

$$kt = -0.46 \left\{ 9.9 \log \frac{\rho}{\rho_0} - 2.65 \log \frac{4.74 - \rho}{4.74 - \rho_0} - 12.5 \log \frac{1 - \rho}{1 - \rho_0} \right\}, \tag{114}$$

where

$$\rho = \frac{\zeta}{0.146}; \qquad \rho_0 = \frac{\zeta_0}{0.146}. \tag{115}$$

It may be well to point out that for a fixed value of $\frac{K_1}{K_2}$ the coefficients in (114) are determined by only one parameter δ which was assigned the value 5 in this example.

For several values of ρ_0 the relation between ρ and (kt) given by equation (114) is plotted in Figure 19a. These curves show a striking similarity in all their characteristic features with the curves of Katz (1937, p. 252), which were obtained by electrical shock stimulation of nerve. In Figures 19b, c and d the time-course of the so-called "local response" and the maximum height of the "local response" respectively are plotted, the latter as a function of the stimulus. This should hold for chemical stimulation. Experiments with which these curves could be checked do not seem to exist yet; at least they are unknown to this author. It would, therefore, be very interesting to attempt to obtain these curves by chemical stimulation of nerve or Nitella, which may be easier experimentally due to smaller speed of response. However, in Figure 20 the theoretical curves for $\frac{K_1}{K_2} = 30$ and $\delta = 4$ describing the time course of the chemical excitability are compared with the corresponding curves of Katz (1937) which describe the time course of the electrical excitability. Figure 19c indicates the presence of a "local response" for values of y which are lower than the concentration of potassium in the resting state. These lower concentrations correspond in the case of electrical stimulation to anodal shocks for which no local response is supposed to occur (Katz 1937). Experimental results of Katz (*loc. cit.*) indicate

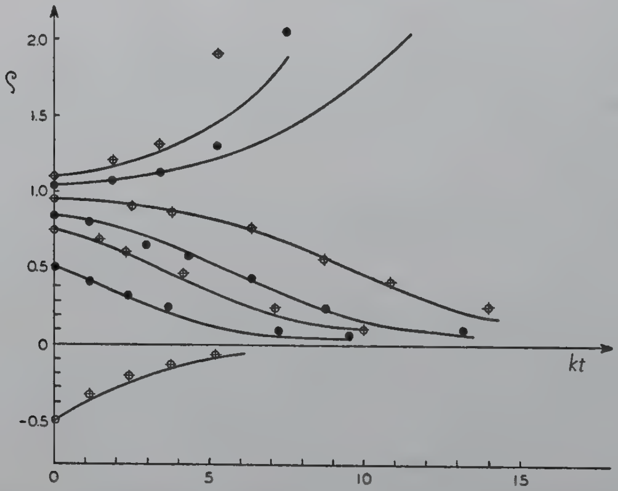

FIGURE 20. Comparison of experimental results (Katz, 1937) with theoretical curves, which were obtained for $\frac{K_1}{K_2} = 30$ and $\delta = 4$ and are described by the equation:

$$kt = -5.32 \log_{10} \frac{\rho}{\rho_0} + 8.45 \log_{10} \frac{1-\rho}{1-\rho_0} - 3.13 \log_{10} \frac{2.7-\rho}{2.7-\rho_0}.$$

the same thing. This corroborates a remark made by Weinberg (1942). As Weinberg (1942) has pointed out so aptly, the only thing which can be concluded from the experimental results is that the phenomenon cannot be described by linear equations. The so-called "local response" which is found for cathodal as well as anodal stimuli is nothing but this deviation from linearity and cannot be interpreted, strictly speaking, on the basis of a phenomenological (Katz, 1937; Rushton, 1937; Weinberg, 1942) theory as had already been pointed out by Weinberg (1942). The theory proposed here, based on a physical mechanism of diffusing potassium ions reacting chemically with a CaP_2 layer, crude as it is, explains these deviations in a plausible way. It predicts that the time constant should be proportional to the square of the intensity of large anodic stimuli. This has not been considered by Weinberg (1942). Actually, the instantaneous time constant of the experimental curves for anodic stimuli (Katz, 1937) do depend on the intensity of those stimuli. However, we have not been able to verify the above-mentioned predicted asymptotic dependence. The reason might be that the experimentally used intensities of the anodic stimuli are not large enough for that purpose.

If the response of the nerve is due to a mechanism such as discussed above, then the so-called "threshold" in Figure 5 of Katz (*loc. cit.*) is no threshold at all. This is seen from our Figure 19b, which is probably more accurate than Katz's figure. Our figure is based on equation (114). The "local response" for $\rho_0 = 0.5$ may not be so slight at all, as shown in our Figure 19b. Therefore, for *this* phenomenon, relation between maxium height of "local response" and intensity of initial stimulus, there seems to be no threshold. On the basis of our theory the real threshold phenomenon would be more hidden; the "local response" derived from it only appears "graded." If experimental results for chemical stimulation confirmed these predictions, it seems to us that those results, together with those of Katz (1937), would suggest a common underlying physical mechanism for excitation by chemical and electrical stimulation. The physical mechanism proposed here, crude as it is, might then be a plausible one, since it is based on the flow of ions which must occur in some way or another in electrical stimulation and may also occur in chemical stimulation, as shown in this work.

It might be interesting to point out here that from the formulae above a dependence of the curves in Figures 19a, b, c and d on, e.g., Ca^{++} and K_2 may be derived in principle. As soon as experimental data are available it would be useful to derive those dependences and compare them with the experimental results to obtain some more clues for improving the theory proposed here. There are obviously several possibilities for this.

Thus what may appear to be a graded local response may actually be due to a "local threshold."

Therefore, we would like to end this part of our work with the conclusion that we do not necessarily have to assume that a threshold for a longitudinal gradient [e.g., the longitudinal polarization, cf. Eichler (1933; Katz, 1939)] is the only part of the threshold essential for excitation, but that the latter may very well be due to a local threshold phenomenon as has been assumed in this work.

Outline of an approximate method for treating the diffusion of ions through the membrane. We will in the remaining part of this paper consider a membrane with a finite thickness λ. However, with a rather good approximation, this may be considered to be small compared with L, if we take the plausible value 10^{-4} cm for L, since λ is of the order of 10^{-6} cm (Davson and Danielli, 1943). (See Figure 21.)

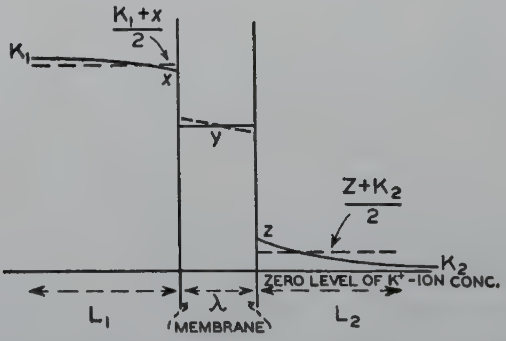

FIGURE 21. Illustration of approximate treatment of the diffusion of K^+ ions through the membrane. The numerals I and II correspond to the vertical "boundaries" in this figure.

To simplify matters we will assume that we may take an average concentration y of the potassium ion in the membrane. Actually we should, of course, consider a gradient of the potassium concentration inside the membrane corresponding to the slanted dotted line between I and II in Figure 21.

Denoting by x and z respectively the concentration of potassium ions at I and II, we find in a similar way as above a description of the system by the following set of differential equations:

$$\frac{L_1}{2}\dot{x}=\frac{D_1}{L_1}(K_1-x)-h'(x-y), \tag{116}$$

$$\lambda\dot{y}=h'(x-y)-h''(y-z), \tag{117}$$

$$\frac{L_2}{2}\dot{z}=h''(y-z)-\frac{D_2}{L_2}(z-K_2), \tag{118}$$

in which h' and h'' are the permeability to potassium ions of I and II respectively.

We are particularly interested in seeing if it is now possible to get a relaxation oscillation with threshold property if we take a linear dependence of the permeability on the potassium ion concentration. The reason for our interest in relaxation oscillations will be clear from the first part of this paper. The linear dependence of the permeability upon the potassium concentration follows, for sufficiently small potassium ion concentrations, from the mechanism illustrated in Figure 3 and described by the corresponding equations (2)—(16), as shown by Figure 4. The above mentioned experimental relation between the conductance of the membrane and the external potassium ion concentration found by Hodgkin (1947) is also more in line with such a dependence than (58). In addition, it would be of some interest if it could be shown that it might be possible to get a threshold phenomenon with such a linear dependence leading to a concave curve as in Figure 4. In other words, to show that a convex curve is not necessary.

Therefore we will now assume

$$h'=C_1x\,, \tag{119}$$

$$h''=C_2z\,. \tag{120}$$

However, before introducing (119) and (120) into (116), (117), and (118) we will reduce the latter system to two first-order nonlinear differential equations. It would be very advantageous if it were possible to solve the set (116), (117), and (118) using such simple assumptions as in (119) and (120), but we have not been able to do so. The main difficulty is that the set (116), (117), and (118) consists of three nonlinear equations. Such third order systems have been solved, as far as we know, only in a few special cases (Friedrichs, 1946; Rauch, 1950). The reduction to a second-order set mentioned above is done in the following way, using our assumption about the smallness of λ relative to L_1 and L_2. Solving (117) for y gives:

$$y = \frac{h'x + h''z - \lambda \dot{y}}{h' + h''}. \tag{121}$$

Substitution of (121) into (116) and (118) yields, after some elementary rearrangements,

$$\frac{L_1}{2}\dot{x} = \frac{D_1}{L_1}(K_1 - x) - \frac{h'h''}{h' + h''}(x - z) - \frac{h'}{h' + h''}\lambda \dot{y} \tag{122}$$

and

$$\frac{L_2}{2}\dot{z} = \frac{h''h'}{h' + h''}(x - z) - \frac{D_2}{L_2}(z - K_2) - \frac{h''}{h' + h''}\lambda \dot{y}. \tag{123}$$

It is interesting to note that in the latter system the harmonic averages of the permeabilities h' and h'' of the two layers I and II occurs essentially as effective "all-over" permeability of the whole membrane, if we neglect the terms with $\dot{y}$ because of the smallness of

$$\frac{\lambda}{L_1} \text{ and } \frac{\lambda}{L_2}.$$

Now introducing (119) and (120) into (122) and (123) we find

$$\frac{L_1}{2}\dot{x} = \frac{D_1}{L_1}(K_1 - x) - \frac{C_1C_2xz}{C_1x + C_2z}(x - z) - \lambda \frac{C_1x}{C_1x + C_2z}\dot{y} \tag{124}$$

and

$$\frac{L_2}{2}\dot{z} = \frac{C_1C_2xz}{C_1x + C_2z}(x - z) - \frac{D_2}{L_2}(z - K_2) - \lambda \frac{C_2z}{C_1x + C_2z}\dot{y}. \tag{125}$$

Adding (124) and (125) leads us to:

$$\frac{L_1}{2}\dot{x} + \frac{L_2}{2}\dot{z} = \left(\frac{D_1}{L_1}K_1 + \frac{D_2}{L_2}K_2\right) - \left(\frac{D_1}{L_1}x + \frac{D_2}{L_2}z\right) - \lambda \dot{y}. \tag{126}$$

Subtraction of (125) from (124) leads to

$$\begin{aligned}\frac{L_1}{2}\dot{x} - \frac{L_2}{2}\dot{z} = {} & \left(\frac{D_1}{L_1}K_1 - \frac{D_2}{L_2}K_2\right) - \left(\frac{D_1}{L_1}x - \frac{D_2}{L_2}z\right) \\ & - \frac{2C_1C_2xz}{C_1x + C_2z}(x - z) - \lambda \frac{C_1x - C_2z}{C_1x + C_2z}\dot{y}.\end{aligned} \tag{127}$$

We now introduce the following new variables:

$$\frac{x+z}{2}=\phi, \tag{128}$$

$$\frac{x-z}{2}=\psi, \tag{129}$$

so that

$$x=\phi+\psi \tag{130}$$

$$y=\phi-\psi. \tag{131}$$

We now find, instead of (126) and (127),

$$\begin{aligned}\frac{L_1+L_2}{2}\dot{\phi}+\frac{L_1-L_2}{2}\dot{\psi}=\left(\frac{D_1}{L_1}K_1+\frac{D_2}{L_2}K_2\right)-\left(\frac{D_1}{L_1}+\frac{D_2}{L_2}\right)\phi\\ -\left(\frac{D_1}{L_1}-\frac{D_2}{L_2}\right)\psi-\lambda\dot{y},\end{aligned} \tag{132}$$

$$\begin{aligned}\frac{L_1-L_2}{2}\dot{\phi}+\frac{L_1+L_2}{2}\dot{\psi}=\left(\frac{D_1}{L_1}K_1-\frac{D_2}{L_2}K_2\right)-\left(\frac{D_1}{L_1}-\frac{D_2}{L_2}\right)\phi\\ +\left(\frac{D_1}{L_1}+\frac{D_2}{L_2}\right)\psi-\frac{4C_1C_2(\phi^2-\psi^2)\psi}{(C_1+C_2)\phi+(C_1-C_2)\psi}\\ -\lambda\frac{(C_1-C_2)\phi+(C_1+C_2)\psi}{(C_1+C_2)\phi+(C_1-C_2)\psi}\dot{y}.\end{aligned} \tag{133}$$

Although unnecessary, we will make the following simplifying assumptions in the remainder of this paper:

$$L_1=L_2=L, \tag{134}$$

$$C_1=C_2=C. \tag{135}$$

Furthermore, for simplification, we shall introduce the following notations:

$$\frac{D_1}{L^2}K_1+\frac{D_2}{L^2}K_2=2\,\Delta_1, \tag{136}$$

$$\frac{D_1}{L^2}K_1-\frac{D_2}{L^2}K_2=2\,\varepsilon_1, \tag{137}$$

$$\frac{D_1}{L^2} = k_1 , \tag{138}$$

$$\frac{D_2}{L^2} = k_2 , \tag{139}$$

$$k_1 + k_2 = \alpha , \tag{140}$$

$$k_1 - k_2 = \beta , \tag{141}$$

$$\frac{\lambda}{L} = \tau , \tag{142}$$

$$\frac{2C}{L} = \gamma . \tag{143}$$

Introduction of (134)—(143) yields the equations:

$$\dot{\phi} = 2\,\Delta_1 - \alpha\,\phi - \beta\,\psi - \tau\,\dot{y} , \tag{144}$$

$$\dot{\psi} = 2\,\varepsilon_1 - \beta\,\phi - \alpha\,\psi - \gamma\,(\phi^2 - \psi^2)\,\frac{\psi}{\phi} - \tau\,\frac{\psi}{\phi}\,\dot{y} . \tag{145}$$

For the special case considered above—(134) and (135)—we obtain from (121), after introducing into the latter (119) and (120) and differentiating,

$$\lambda\,\dot{y} = \lambda\,\frac{\dot{\phi}\,(\phi^2 - \psi^2) + \dot{\psi}\,2\,\phi\,\psi}{\phi^2} , \tag{146}$$

if we neglect powers of λ higher than the first one.

From (144), (145), and (146) we obtain the following equations linear in $\dot{\phi}$ and $\dot{\psi}$:

$$\left(1 + \tau\,\frac{\phi^2 - \psi^2}{\phi^2}\right)\dot{\phi} + 2\,\tau\,\frac{\psi}{\phi}\,\dot{\psi} = 2\,\Delta_1 - \alpha\,\phi - \beta\,\psi , \tag{147}$$

$$\tau\,\frac{(\phi^2 - \psi^2)\,\psi}{\phi^3}\,\dot{\phi} + \left(1 + 2\,\tau\,\frac{\psi^2}{\phi^2}\right)\dot{\psi} = 2\,\varepsilon_1 - \beta\,\phi - \alpha\,\psi - \gamma\,\frac{(\phi^2 - \psi^2)\,\psi}{\phi} . \tag{148}$$

These equations can be solved for $\dot{\phi}$ and $\dot{\psi}$. The solutions are of the form:

$$\dot{\phi}=F(\phi,\psi,\tau,\alpha,\beta,\gamma,\Delta_1,\varepsilon_1), \tag{149}$$

$$\dot{\psi}=G(\phi,\psi,\tau,\alpha,\beta,\gamma,\Delta_1,\varepsilon_1). \tag{150}$$

In principle we can obtain from the set (149) and (150) a second-order equation e.g. in ψ by elimination of ϕ. To make use of that equation we must introduce drastic approximations. Explicit calculation of F in (149) leads to:

$$\dot{\phi}=\frac{2\,\Delta_1}{L}-\frac{\alpha}{L}\phi-\frac{\beta}{L}\psi+\tau(.\ \ .\ \ .\ \ .). \tag{151}$$

Neglecting as a zero approximation the terms in τ in this equation, τ being small according to our assumptions, we obtain:

$$\phi=\frac{2\,\Delta_1}{L}-\frac{\alpha}{L}\phi-\frac{\beta}{L}\psi. \tag{152}$$

Assuming $\beta/\alpha << 1$ we have

$$\dot{\phi}=\frac{2\,\Delta_1}{L}-\frac{\alpha}{L}\phi, \tag{153}$$

which is similar to (31).

As in (31) we find as the steady state value for ϕ:

$$\phi=\frac{2\,\Delta_1}{\alpha}=\Delta_2, \tag{154}$$

which we will keep as our first approximation for ϕ.

Introducing

$$\frac{\phi}{\Delta_2}=\eta, \tag{155}$$

$$\frac{\psi}{\Delta_2}=\xi, \tag{156}$$

we find from (154)

$$\eta=1. \tag{157}$$

We obtain for ξ an equation of the form:

$$\dot{\xi} = k\frac{P_5(\eta\,,\,\xi)}{P_3(\eta\,,\,\xi)}, \tag{158}$$

in which $P_5(\eta\,,\,\xi)$ and $P_3(\eta\,,\,\xi)$ are polynomials of the order 5 and 3 in ξ respectively.

By differentiating both sides of (158) we obtain

$$\ddot{\xi} - k\frac{\dfrac{\partial P_5}{\partial \xi}P_3 - P_5\dfrac{\partial P_3}{\partial \xi}}{P_3^{\,2}}\dot{\xi} - k\frac{\dfrac{\partial P_5}{\partial \eta}P_3 - P_5\dfrac{\partial P_3}{\partial \eta}}{P_3^{\,2}}\dot{\eta} = 0. \tag{159}$$

Substituting in this equation (157) and an approximation for $\dot{\eta}$ higher than that corresponding to (157), we finally obtain:

$$\ddot{\xi} + \Phi(\xi)\dot{\xi} + \Psi(\xi) = 0\,. \tag{160}$$

At the present stage of development, both experimental and theoretical, it is hardly worthwhile to derive explicitly the expressions for $\Phi(\xi)$ and $\Psi(\xi)$. Though this field of mathematics is momentarily in a rapid rate of progress, as shown by recent work (Andronow and Chaikin, 1937; Minorsky, 1947; Stoker, 1950; Lefshetz, 1950; Kryloff and Bogoliuboff, 1934), the theory for the case in which $\Phi(\xi)$ and $\Psi(\xi)$ are both of higher order in ξ than the first does not seem to be in a form that is ready for application. In a former paper (Karreman, 1949) the author showed (as mentioned in the first part of this paper it had been shown earlier) that in the case in which $\Psi(\xi)$ is proportional to ξ, a relaxation oscillation with threshold can be obtained when $\Phi(\xi)$ is at least of the fourth degree and $\Phi(\xi) = 0$ has at least two appropriate positive and two appropriate negative roots. Although in our present case $\Psi = \Psi(\xi)$ is much more complicated, even in the lowest approximation, we still believe (although we have no proof) that for a self-sustained oscillation it is necessary, in general, for the function $\Phi = \Phi(\xi)$ to be negative for sufficiently long intervals of positive values of ξ and also negative values of ξ. It is interesting now to note that for the special case treated above [see eqs. (134) and (135)] $\Phi(\xi)$ can be shown to have for small τ the following form:

$$\begin{aligned}\Phi(\xi) = k\{&(1+\mu)(1+2\,\tau) + 2\,\tau(z-3\,\pi)\,\xi \\ &-[3\,\mu + 2\,\tau(2+5\,\mu)]\,\xi^2 + 4\,\tau\,\pi\,\xi^3 \\ &+ 4\,\tau\,\mu\,\xi^4\}/\{1+\tau(1+\xi^2)\}^2\,.\end{aligned} \tag{161}$$

The dimensionless constants are given by

$$\mu = \frac{\gamma \Delta_2}{a}, \tag{162}$$

$$z = \frac{\varepsilon_1}{\Delta_1}, \tag{163}$$

$$\pi = \frac{\beta}{a}, \tag{164}$$

$$k = a, \tag{165}$$

together with (136), (137), (140), and (141).

It is easy to see that $\Phi(\xi) = 0$ has for small τ two positive and two negative roots and has a form similar to that shown in Figure 22, if μ is sufficiently large (z and π being both less than 1, the latter only in absolute value).

Depending on the relative position of the four roots ξ_1, ξ_2, ξ_3, and ξ_4 the situation shown in Figure 22 may lead to the following two cases:

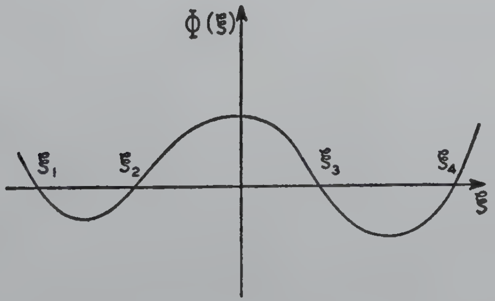

FIGURE 22

1. Only a damped oscillation occurs below a certain "critical" finite disturbance (corresponding to a threshold), if none of the regions of negative damping is reached by it from the original equilibrium state.

2. If the disturbance, above a certain threshold, from the original equilibrium state is such that at least one of the regions has been reached, two things may happen depending upon the circumstances:

a. The regions of negative damping are so far apart that even if self-excited in one of such regions the ξ is damped so much in the intermediate region that it does not reach the other region (cf. Karreman, 1949, where it was shown that in a similar situation; namely, of one region of negative damping, the oscillation was always damped). This would correspond to one spike.

b. The regions of negative damping are sufficiently close so that an undamped threshold oscillation occurs, corresponding to repetitive discharges.

In this way we see that a mechanism such as proposed here might account for a spike as well as an oscillation, both with threshold properties. It is interesting to note that the parameter μ, the relative order of magnitude of which was found to be important above, is determined by the Ca^{++} ion concentration. Rough estimations, taking into account the order of magnitude of the values of a, $\boldsymbol{P}_0$ and the equilibrium constants $\boldsymbol{K}_1$ and $\boldsymbol{K}_2$ in (16) and (14) show that C_i in (119), (120), and (135) is approximately inversely proportional to $\sqrt{(Ca^{++})}$. Because of (143) and (162) the same holds true for μ. We noticed above that μ has to be sufficiently large, particularly if we realize that the four roots discussed above have to be within the physiological limits, which cannot be so easily obtained any longer. Therefore, theoretically we might be led to expect relaxation oscillations for a sufficiently small value of Ca^{++}, which is in agreement with experimental evidence (Brink and others, 1946) in the case of nerve fibers.

Discussion. In a very simple way an attempt has been made to investigate quantitatively the consequences of structural changes in a membrane due to chemical reactions of K^+ ions and a layer consisting of $Ca\mathbf{P}_2$ compound through which K^+ ions diffuse. On the basis of these chemical reactions and a "hole" concept, a quantitative definition of the permeability of the membrane, which is supposed to have as an essential element such a $Ca\mathbf{P}_2$ layer, to K^+ ions is given. Several possibilities for this have been indicated. One, namely that the permeability of the membrane is proportional to the sum of the concentrations of the formed KP and of the $\mathbf{P}^-$, is elaborated. Equations describing the diffusion of K^+ ions are given with the aid of the approximation method for the case in which the membrane is supposed to have finite thickness and at one or both sides such a $Ca\mathbf{P}_2$ layer. In the last part of this paper we have indicated that this explicit consideration of the finite thickness of the membrane leads to nonlinear differential equations which are not amenable to solution at the present time. However there seems to be some indication that they may lead to equations describing relaxation oscillations with threshold properties in qualitative agreement with experimental facts, for instance, as far as the dependence of (Ca^{++}) is concerned. If it is possible in the future to determine the frequency dependence it may be that theoretically observed properties such as frequency demultiplication and dependence of the frequency on (Ca^{++}) can be determined. However since this is a program for the future, a similar mechanism based on the ionization of a $Ca\mathbf{P}_2$ layer has been assumed in the central part of this paper as responsible for the determination of the permeability of a membrane whose thickness has been neglected for reasons of mathematical simplicity in the equations describing the diffusion of K^+ ions through it. At the same time some electrical effects due to an applied external electrical field and a "resting potential" across the membrane, using for the latter a diffusion potential of K^+ ions, on the chemical reactions of the CaP_2 layer are taken into account. For mathematical simplicity other electrical effects such as electrical forces on the diffusing K^+ ions, the effects of other ions (e.g., Ca^{++}) on the potential across the membrane, as well as the diffusion of other ions (e.g., Ca^{++} and anions) have been neglected. These omissions, particularly the first two, are thought to be serious shortcomings. On the basis of such a mechanism the permeability of the membrane to K^+ ions is determined. Explicit relations for the dependence of the membrane permeability on an externally applied electrical field, on the Ca^{++} ion concentration, on the average K^+ ion concentration level have been derived in principle. The dependence of the permeability to potassium ions on the K^+ ion concentration is used in the differential equations describing the diffusion of the K^+ ions through the membrane. The latter equations are solved under the assumption that the average K^+ ion concentration has its steady state value. The solution shows threshold properties under certain circumstances. Estimations of "resting potential," threshold (chemical as well as electrical), "action potential," permeability increase, and electrical field across the CaP_2 layer are made and shown to have the correct order of magnitude. A possible way to derive the one-factor theory is outlined. Also, the time course of the excitatory state for various intensities of an initial chemical stimulus has been derived theoretically from the proposed physical mechanism. The curves obtained show all the characteristic features of the corresponding ones for electrical stimulation. It is pointed out, therefore, that these results suggest that response to both electrical and chemical stimulation is based on a common threshold phenomenon as proposed here, which may very well be a local process. Furthermore it is pointed out that the dependence of the latter curves on external parameters such as the Ca^{++} ion and the external K^+ ion concentration may be determined in principle. A more general treatment based on a more general dependence of the permeability to K^+ ions on the local K^+ ion concentration is given and applied to derive the relation between the electrical threshold and the K^+ ion concentration on the outside. Other applications to derive relations between the chemical threshold, the Ca^{++} ion concentration, and the applied electrical potential are made. The dependence of the electrical threshold on the Ca^{++} ion concentrations has been derived theoretically. Comparison of the result obtained with the corresponding experimental result shows that the former gives a more sensitive dependence of the threshold on the Ca^{++} ion concentration. This may be due to the fact that no accommodation effects have been considered theoretically, that the theoretical result refers to local stimulation, and that the threshold derivation neglects the diffusion of Ca^{++} itself as well as the influence of Ca^{++} on the potential difference across the CaP_2 layer considered. Also a current-voltage characteristic has been derived and is compared with the one experimentally obtained. The differences are ascribed to accommodation effects. The possibility of obtaining the dependence of these curves on Ca^{++} ion and external K^+ ion concentration is mentioned. Additional relations which may be predicted on the basis of this theory are the increase in permeability to K^+ ions during activity as a function of the external K^+ ion concentration, of the Ca^{++} ion concentration and of the applied electrical potential (ΔV) (cathodic as well as anodic). These possible extensions all call for more experimentation along these lines.

Though there is a possible manner in which metabolic reactions may be taken into account, namely, through a change in $\boldsymbol{P}_0$ in equations (8) and (44), they have been neglected above because it was supposed that the metabolic reactions may be assumed to be relatively slow compared with the ionic reactions. Therefore, recovery processes have not been taken into account. It may be worth mentioning here that a mechanism as proposed by E. Eriksson (1949) might perhaps be applied here, the breakdown of the CaP_2 layer as obtained here giving an increase in the P^- anion concentration.

The duration of the development of the action potential could not be determined theoretically on the basis of this mechanism. It seems plausible that the mechanism outlined for obtaining relaxation oscillations might be better in this respect. However, it should be stressed here that the considerations about the relaxation oscillations in the latter part of this paper are only suggestive and might be a starting point for more detailed investigations, complicated as they are. However, they are by no means conclusive and, as will be obvious from the outline given above, they constitute no proof whatsoever. Particularly this holds as long as the physiological limits and, especially, the range of validity of the approximations made have not been determined yet.

Finally, we would like to point out that while we have tried to give an underlying physical picture for changes in permeability to K^+ ions, formally similar mathematical considerations may describe other dependences of the permeability on the K^+ ion concentration or the same, or similar, dependence based on another picture. Furthermore, it might be that similar considerations may apply to ions other than the ion we called the K^+ ion.

Summary.

1. On the basis of the assumption that an essential element of a membrane is a CaP_2 layer, an expression for the permeability of the membrane to K^+ ions diffusing through it and reacting chemically with it has been derived theoretically, taking into account some electrical effects due to the diffusion potential of the K^+ ions and an externally applied electrical potential difference on the chemical reactions.

2. A relation between the permeability to K^+ ions and the concentration of the K^+ ions outside the membrane has been derived, which shows the influence of some factors [Ca^{++} ion concentration, externally applied electrical field (ΔV)] on the former.

3. A threshold of the right order of magnitude is shown to exist for the amount of K^+ ions locally applied to the membrane in order to excite. Also a threshold for parametric electrical stimulation is shown to exist and to have the correct order of magnitude. A way to derive the dependence of the chemical threshold on the Ca^{++} ion concentration has been given. The degree of depolarization of the membrane as calculated here is adequate.

4. Correct orders of magnitude are found on this basis for the resting potential, thresholds, permeability increase, and intensity of the electric field strength across the CaP_2 layer.

5. A possible way to derive the one-factor theory of excitation is indicated.

6. A method is outlined to obtain in principle the time course of the excitatory disturbance and of the local response.

7. A way to obtain relaxation oscillations on the basis of a similar mechanism is outlined.
8. Derivations of other possible relationships are indicated.

It is a great pleasure for the author to express his indebtedness to all members of the Committee on Mathematical Biology for their interest and help during the years he has been studying under their guidance. He wants to thank Professor N. Rashevsky and Prof. H. G. Landau. Professor H. D. Landahl's continued interest, his many helpful, stimulating and encouraging suggestions during the course of preparation of this thesis are gratefully appreciated by the author. The author also wishes to express his great indebtedness to Mrs. Carlton Smith for the very painstaking task of the preparation of this manuscript.

LITERATURE

Andronow, A. A. and C. E. Chaikin. 1949. *Theory of Oscillations.* (English Language Ed. by S. Lefshetz.) Princeton: Princeton University Press. (Russian Ed., 1937.)

Arvanitaki, A. 1938a. *Propriétés Rhythmiques de la Matière Vivante. I. Étude Expérimentale sur les nerfs isolés d'invertébrés.* Paris: Hermann & Cie.

———. 1938b. *Propriétés Rhythmique de la Matière Vivante. II. Étude Expérimentale sur le Myocarde d'Helise.* Paris: Hermann & Cie.

———. 1939. "Recherches sur la Réponse Oscillatoire Locale de l'Axone Géant Isolé de 'Sepia'." *Archiv. Intern. de Physiol.,* 49, 209–56.

Auger, D. 1936. *Comparaison entre la Rythmicité des Courants d'Action Cellulaires chez les Végétaux & chez les Animaux.* Paris: Hermann & Cie, Ed.

Bear, R. S. and F. O. Schmitt. 1939. "Electrolytes in the Axoplasm of the Giant Nerve Fibers of the Squid." *Jour. Cell. Comp. Physiol.,* 14, 205–15.

Bernstein, J. 1902. "Untersuchungen zur Thermodynamik der bioelektrischen Ströme." *Pflüg. Arch. f.d. ges. Physiol.,* 92, 521–62.

Bethe, A. 1937. "Rhythmik und Periodik besonders im Hinblick auf die Bewegungen des Herzens und der Meduse." *Pflüg. Arch.,* 239, 41–73.

———. 1943. "Die periodische Unterbrechung rhythmischer Vörgange im Vergleich zu ähnlichen Vorgängen an elektrischen Kipp systemen." *Ibid.,* 246, 485–519.

——— and H. Schaefer. 1947. "Erregungsgesetze einer Blinkschaltung im Vergleich zu denen biologischen Objekte." *Pflüg. Arch.,* 249, 313–38.

Bonhoeffer, K. F. 1948a. "Activation of Passive Iron as a Model for the Excitation of Nerve." *Jour. Gen. Physiol.,* 32, 69–91.

———. 1948b. "Über periodische chemische Reaktionen I." *Zeitschr. f. Elektroch. und angew. physik Chem.,* 51, 24–9.

——— et al. 1948c. "Über periodische chemische Reaktionen II." *Zeitschr. f. Elektroch. und angew physik. Chem.,* 51, 29–37

——— et al. 1948d. "Über periodische Reaktionen III." *Ibid.,* 52, 60–7.

——— et al. 1948e. "Über periodische Reaktionen IV." *Ibid.,* 52, 67–72.

——— et al. 1948f. "Über periodische Reaktionen V." *Ibid.*, 52, 149–60.

Brink, F. and others. 1946. "Chemical Excitation of Nerve." *Ann. N. Y. Acad. Sci.*, 47, 457–85.

Cole, K. S. and H. J. Curtis. 1938. "Impedance of Nitella during Activity." *Jour. Gen. Physiol.*, 22, 37–64.

———. 1939. "Impedance of the Squid Axon during Activity." *Ibid.*, 22, 649–70.

———. 1940. "Membrane Potential of the Squid Giant Axon during Current Flow." *Ibid.*, 24, 551–63.

Danielli, J. F. and H. Davson. 1935. "A Contribution to the Theory of Thin Films." *Jour. Cell. and Comp. Physiol.*, 5, 495–508.

Davson, H. and J. F. Danielli. 1943. *The Permeability of Natural Membranes.* Cambridge: University Press.

Eichler, W. 1933. "Schwelle, Akkommodation und elektrotonische Erregbarkeitsänderung des Nerven als Phänomene der Erregungsleitung." *Zeitchr. f. Biol.*, 93, 407–58.

Engström, A. and H. Lütky. 1950. "Distribution of mass and lipids in the nerve fiber." *Exp. Cell. Res.*, 1(1), 81–91.

Eriksson, E. 1949. "Ionic Diffusion through Membranes." *Ann. Roy. Agric. Coll. Sweden*, 16, 420–40.

Fessard, A. 1931. "Les Rythmes Nerveuse et les Oscillations de Relaxation." *L'Année Psychol.*, 32, 49–117.

———. 1936a. *Propriétés Rythmiques de la Matière Vivante I. Nerfs Isolés* (1). *Nerfs Myélinisés.* Paris: Hermann & Cie.

———. 1936 b. *Propriétés Rythmiques de la Matière Vivante II. Nerfs Isolés* (2). Nerfs non Myélinisés. Paris: Hermann & Cie.

Fleckenstein, A. 1942. "Beitrag zum Mechanismus der Muskelkontraktion und zur Entstehung der Aktionströme." *Pflüg. Arch. f.d. ges. Physiol.*, 246, 411–27.

Friedrichs, K. O. 1946. *On Nonlinear Vibrations of Third Order.* New York: New York Univ. Inst. for Math. and Mech.

Fulton, J. F. 1947. *Howell's Textbook of Physiology.* Philadelphia and London: Saunders Co.

Heilbrunn, L. V. 1943. *An Outline of General Physiology.* Philadelphia and London: Saunders Co.

Hill, S. E. and W. J. V. Osterhout. 1934. "Nature of the Action Current in Nitella. II." *Jour. Gen. Physiol.*, 18, 377–83.

———. 1937. "Calculations of Bioelectric Potentials II." *Ibid.*, 21, 541–56.

———. 1938. "Nature of the Action Current in Nitella IV." *Ibid.*, 22, 91–100.

Höber, R. 1945. *Physical Chemistry of Cells and Tissues.* Philadelphia and Toronto: The Blakiston Co.

Hodgkin, A. L. 1947. "The Effect of Potassium on the Surface Membrane of an Isolated Axon." *Jour. Physiol.*, 106, 319–40.

———. 1949. "Ionic Exchange and Electrical Activity in Nerve and Muscle." *Arch. des. Sci. Physiol.*, III, 151–64.

——— and A. F. Huxley. 1947. "Potassium Leakage from an Active Nervefiber." *Jour. Physiol.*, 106, 341–66.

———, A. F. Huxley and B. Katz. 1949. "Ionic Currents Underlying Activity in the Giant Axon of the Squid." *Arch. des Sci. Physiol.*, III, 129–50.

Jordan, P. 1944. "Quantenphysik und Biologie." *Naturwissenschaften*, 32, 309–16.

Karreman, G. 1949. "Some Types of Relaxation Oscillations as Models of All-or-none Phenomena." *Bull. Math. Biophysics*, 11, 311–18.

Katz, B. 1937. "Experimental Evidence for a non-conducted Response of Nerve to Subthreshold Stimulation." *Proc. Roy. Soc. B.*, 124, 244–76.

———. 1939. *Electric Excitation in Nerve.* London: Oxford University Press.

———. 1947. "Subthreshold Potentials in Medullated Nerve." *Jour. Physiol.*, 106, 66–79.

Krylov, N. and N. Bogoliuboff. 1949. *Introduction to Non-Linear Mechanics.* (English Ed. by S. Lefschetz.) Princeton: Princeton University Press. (Ukran Eds., 1934 and 1937.)

Lefshetz, S. 1950. *Contributions to the Theory of Non-Linear Oscillations.* Princeton: Princeton University Press.

Lillie, R. S. 1923. *Protoplasmic Action and Nervous Action.* Chicago: University of Chicago Press.

———. 1924. "Factors Affecting Transmission and Recovery in the Passive Iron Nerve Model." *Jour. Gen. Physiol.*, 7, 473–507.

McLean, F. C. and A. B. Hastings. 1935. "The State of Calcium in the Fluids of the Body." *Jour. Biol. Chem.*, 108, 285–322.

Minorsky, N. 1947. *Introduction to Non-Linear Mechanics.* Ann Arbor: J. W. Edwards.

von Muralt, A. 1946. *Die Signalübermittlung im Nerven.* Basel: Verlag Birkhäuser.

Osterhout, W. J. V. 1933. "Anesthesia in Acid and Alkaline Solution." *Jour. Gen. Physiol.*, 17, 99–103.

———. 1934. "Nature of the Action Current in Nitella I." *Ibid.*, 18, 215–27.

———. 1949. "Some Bioelectrical Problems." *Proc. Nat. Acad. Sci.*, 35, 548–58.

——— and S. E. Hill. 1934. "The Nature of the Action Current in Nitella III." *Jour. Gen. Physiol.*, 18, 499–514.

Poincaré, H. 1892. *Les méthodes nouvelles de la mécanique céleste I.* Paris: Gauthier-Villars.

van der Pol, B. 1926. "On Relaxation Oscillations." *Philosophical Mag.*, 2, November.

——— and M. J. van der Mark. 1928. "Le battement du coeur considéré comme oscillation de relaxation et un modèle électrique du coeur." *L'Onde Electrique*, 7, 365–93.

Rapoport, A. 1950. "Contribution to the Probabilistic Theory of Neural Nets: II. Facilitation and Threshold Phenomena." *Bull. Math. Biophysics*, 12, 187–97.

Rashevsky, N. 1948. *Mathematical Biophysics.* Rev. Ed. Chicago: University of Chicago Press.

Rauch, L. L. 1950. "Oscillation of a Third Order Nonlinear Autonomous System." *Contributions to the Theory of Nonlinear Oscillations* (Ed. S. Lefshetz). Princeton: Princeton University Press.

Rushton, W. A. H. 1932. "A New Observation in the Excitation of Muscle and Nerve." *Jour. Physiol.*, 75, 16P.

———. 1937. "Initiation of the Propagated Disturbance." *Proc. Roy. Soc. B*, **124**, 210–43.

Schaefer, H. 1940. *Elektrophysiologie I.* Wien: Frans Deuticke.

Schäfer, O. 1943. "Untersuchung an einer Schaltung zur Erzeugung ein-und aussetsender Kippschwingungen." *Pflüg. Arch. f.d. ges. Physiol.*, **246**, 520–24.

von Schelling, H. 1944. "Das All-order-Nichts-Gesetz, gedentet als Endergebnis einer Auslösungsfolge." *Abh. d. Prensz. Akad. d. Wissensch*, Nr. 6.

Stoker, J. J. 1950. *Nonlinear Vibrations in Mechanical and Electrical Systems.* New York and London: Interscience Publishers.

Tasaki, I. 1940. "Mikrophysiologische Untersuchung über die Grundlage der Erregungsleitung in der markhaltigen Nervenfaser." *Pflüg. Arch. f.d. ges. Physiol.*, **244**, 125–41.

——— and T. Takeuchi. 1941. "Der am Ranvierschen Knoten entstehende Aktionsstrom und seine Bedentung für die Erregungsleitung." *Pflüg. Arch. f.d. ges. Physiol.*, **244**, 696–711.

Verwey, E. J. W. and J. Th. G. Overbeek. 1948. *Theory of the Stability of Lyophobic Colloids.* Amsterdam and New York: Elsevier.

Webb, D. A. and J. Z. Young. 1940. "Electrolyte content and action potential of the giant nerve fibres of Loligo." *Jour. Physiol.*, **98**, 299–313.

Weinberg, A. M. 1942. "Non-linear Excitation Theory: Non-Accommodative, Sub-Threshold Effects." *Bull. Math. Biophysics*, **4**, 33–44.